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(54) Title: HDAC9 POLYPEPTIDES AND POLYNUCLEOTIDES AND USES THEREOF

(57) Abstract: The present invention features substantially pure HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), an HDRP(Δ NLS) polypeptides, and isolated nucleic acid molecules encoding those polypeptides. The present invention also features vectors containing HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS) nucleic acid sequences, and cells containing those vectors.

HDAC9 POLYPEPTIDES AND POLYNUCLEOTIDES AND USES THEREOF

RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No.

- 5 60/298,173 filed on June 14, 2001, U.S. Provisional Application No. 60/311,686 filed on August 10, 2001, and U.S. Provisional Application No. 60/316,995, filed on September 4, 2001. The entire teachings of the above applications are incorporated herein by reference.

10 GOVERNMENT SUPPORT

The invention was supported, in whole or in part, by grant CA-0974823 from the National Cancer Institute. The Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

- 15 The N-terminal tails of core histones are covalently modified by post-translational modifications, including acetylation and phosphorylation. Evidence suggests that these covalent modifications play important roles in several biological activities involving chromatin, *e.g.*, transcription and replication. Histone deacetylases (HDACs) catalyze the removal of the acetyl group from the lysine
20 residues in the N-terminal tails of nucleosomal core histones resulting in a more compact chromatin structure, a configuration that is generally associated with repression of transcription.

- Five proteins and/or open reading frames in yeast (RPD3, HDA1, HOS1, HOS2 and HOS3) that share significant homology in the catalytic domain have been
25 identified as HDACs based upon their sequence homology to human HDAC1. To date, eight HDACs have been identified in mammalian cells, and classified into two classes based on their structure and similarity to yeast RPD3 or HDA1 proteins. Recently, Sir2 family proteins that are structurally unrelated to the five proteins aforementioned have been identified as NAD-dependent HDACs. Class I HDACs
30 are the yeast RPD3 homologs HDAC1, 2, 3, and 8, and are composed primarily of a catalytic domain. Class II HDACs are the yeast HDA1 homologs HDAC4, 5, 6; and

7. HDAC4, 5, and 7 contain a long non-catalytic N-terminal end and a C-terminal HDAC catalytic domain while HDAC6 has two HDAC catalytic domains.

It has also been determined that histone deacetylases can be sensitive to small molecules, including trichostatin A (TSA), trapoxin, and butyrate. For example, the yeast RPD3 and HDA1 and mammalian HDAC1, 2, 3, 4, 5, 6, 7 and 8 are sensitive to inhibition by trichostatin A (TSA). The Sir2 family HDACs, yeast HOS3 and *Drosophila melanogaster* dHDAC6, however, appear to be relatively insensitive to TSA. A class of hybrid bipolar compounds, such as suberoylanilide hydroxamic acid (SAHA) have also been shown to inhibit histone deacetylases and induce terminal differentiation and/or apoptosis in various transformed cells. Examples of such compounds can be found in U.S. Patent Nos. 5,369,108, issued on November 29, 1994, 5,700,811, issued on December 23, 1997, and 5,773,474, issued on June 30, 1998 to Breslow *et al.*, as well as U.S. Patent Nos. 5,055,608, issued on October 8, 1991, and 5,175,191, issued on December 29, 1992 to Marks *et al.*, the entire content of all of which are hereby incorporated by reference.

The identification of the mechanisms by which histones are deacetylated, and the characterization of histone deacetylase function would be of great benefit in understanding how gene transcription is controlled, how the cell cycle is regulated, and how cells are signaled to undergo terminal differentiation and/or apoptosis. Elucidation of such mechanisms can lead to improved therapeutics for many diseases, in particular those characterized by cell proliferation or a lack of cell differentiation or apoptosis, for example, cancer.

SUMMARY OF THE INVENTION

25 The present invention relates to isolated or recombinant histone deacetylase polypeptides, and isolated histone deacetylase nucleic acid molecules encoding those polypeptides, as well as vectors and cells containing those isolated nucleic acid molecules.

In one aspect of the invention, the isolated or recombinant histone deacetylase polypeptide is selected from a) an isolated or recombinant polypeptide comprising SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; and b) a polypeptide having at least 60% sequence identity with any one

of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. In one embodiment, the isolated or recombinant histone deacetylase polypeptide consists of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. In another embodiment, the isolated or recombinant histone deacetylase polypeptide is mammalian; preferably, the isolated or recombinant histone deacetylase polypeptide is human.

In another aspect, the invention features an isolated nucleic acid molecule selected from a) an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9; b) a complement of an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9; c) an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; d) a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; e) a nucleic acid that is hybridizable under high stringency conditions to a nucleic acid molecule that encodes any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, or SEQ ID NO: 8, or a complement thereof; or f) a nucleic acid molecule that is hybridizable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, or SEQ ID NO: 7; and g) an isolated nucleic acid molecule that has at least 55% sequence identity with any one of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or a complement thereof. In one embodiment, the isolated nucleic acid molecule consists of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9. In another embodiment, the isolated nucleic acid molecule is mammalian; preferably, the isolated nucleic acid molecule is human.

In other aspects, the invention features a vector comprising the isolated histone deacetylase nucleic acid molecule described above, a cell comprising the vector, and a cell comprising the isolated histone deacetylase nucleic acid molecule described above.

In another aspect, the invention features a purified antibody that selectively binds a histone deacetylase polypeptide described above.

In yet another aspect, the invention features a method of identifying a compound that modulates expression of a histone deacetylase nucleic acid molecule described above. The method comprises the steps of a) contacting the nucleic acid molecule with a candidate compound under conditions suitable for expression; and
5 b) assessing the level of expression of the nucleic acid molecule. A candidate compound that increases or decreases expression of the nucleic acid molecule relative to a control is a compound that modulates expression of the nucleic acid molecule. In one embodiment, the method is carried out in a cell or animal. In another embodiment, the method is carried out in a cell free system.

10 The invention also features a method of treating a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, for example, cancers such as lymphoma, leukemia, melanoma, ovarian cancer, breast cancer, pancreatic cancer, prostate cancer, colon cancer, and lung cancer and myeloproliferative disorders, including polycythemia vera, essential thrombocythemia, agnogenic myeloid
15 metaplasia, and chronic myelogenous leukemia in an individual, comprising administering a compound identified by the above method.

In still another aspect, the invention features a method of identifying a compound that modulates the enzymatic activity of the histone deacetylase polypeptide described above. The method comprises the steps of a) contacting the
20 polypeptide with a candidate compound under conditions suitable for enzymatic reaction; and b) assessing the activity level of the polypeptide. A candidate compound that increases or decreases the activity level of the polypeptide relative to a control is a compound that modulates the enzymatic activity of the polypeptide. In one embodiment, the method is carried out in a cell or animal. In another
25 embodiment, the method is carried out in a cell free system.

In yet another embodiment, the polypeptide is further contacted with a substrate for the polypeptide, wherein the substrate is selected from the group consisting of a cell proliferation disease binding agent, an apoptotic disease binding agent, and a cell differentiation disease binding agent. In one embodiment, the
30 candidate compound is an inhibitor. In another embodiment, candidate compound is an activator.

In another aspect, the invention features a method of identifying a compound that modulates the transcriptional repression activity of the histone deacetylase polypeptide described above. The method comprises the steps of a) contacting the polypeptide with a candidate compound under conditions suitable for a
5 transcriptional repression reaction; and b) assessing the transcriptional repression activity level of the polypeptide. A candidate compound that increases or decreases the transcriptional repression activity level of the polypeptide relative to a control is a compound that modulates the transcriptional repression activity of the polypeptide. In one embodiment, the method is carried out in a cell or animal. In another
10 embodiment, the method is carried out in a cell free system.

In yet another embodiment, the polypeptide is further contacted with a substrate for the polypeptide, wherein the substrate is selected from the group consisting of a cell proliferation disease binding agent, an apoptotic disease binding agent, and a cell differentiation disease binding agent. In one embodiment, the
15 candidate compound is an inhibitor. In another embodiment, candidate compound is an activator.

In another aspect, the invention features a method of identifying a compound that modulates expression of a histone deacetylase nucleic acid molecule described above. The method comprises the steps of a) providing a nucleic acid molecule
20 comprising a promoter region of the histone deacetylase nucleic acid molecule described above, or part of such a promoter region, operably linked to a reporter gene; b) contacting the nucleic acid molecule or with a candidate compound; and c) assessing the level of the reporter gene. A candidate compound that increases or decreases expression of the reporter gene relative to a control is a compound that
25 modulates expression of the histone deacetylase nucleic acid molecule described above. In one embodiment, the method is carried out in a cell.

In still another aspect, the invention features a method of identifying a polypeptide that interacts with a histone deacetylase polypeptide described above in a yeast two-hybrid system. The method comprises the steps of a) providing a first
30 nucleic acid vector comprising a nucleic acid molecule encoding a DNA binding domain and the histone deacetylase polypeptide described above; b) providing a second nucleic acid vector comprising a nucleic acid encoding a transcription

activation domain and a nucleic acid encoding a test polypeptide; c) contacting the first nucleic acid vector with the second nucleic acid vector in a yeast two-hybrid system; and d) assessing transcriptional activation in the yeast two-hybrid system. An increase in transcriptional activation relative to a control indicates that the test
5 polypeptide is a polypeptide that interacts with the histone deacetylase polypeptide described above.

The invention also features a pharmaceutical composition comprising a histone deacetylase polypeptide described above.

In addition, the present invention features a method of diagnosing a cell
10 proliferation disease, an apoptotic disease, or a cell differentiation disease in a subject. The method comprises the steps of a) obtaining a sample from the subject; and b) assessing the level of activity or expression of the histone deacetylase polypeptide described above or the level of the nucleic acid molecule described above in the sample. If the level is increased relative to a control, then the subject
15 has an increased likelihood of having a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, and if the level is decreased relative to a control, then the subject has a decreased likelihood of having a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. In one embodiment, the polypeptide level is assayed using immunohistochemistry techniques. In another
20 embodiment, the nucleic acid molecule level is assayed using *in situ* hybridization techniques.

Compounds and/or polypeptides identified in the above-described screening methods are also part of the present invention.

25 DESCRIPTION OF THE FIGURES

FIG. 1 is a schematic representation of the order in which FIGS. 1A-1O should be viewed.

FIGS. 1A-1C show the cDNA sequence of *HDAC9* (SEQ ID NO: 1). The arrows and numbers in the *HDAC9* sequence indicate exons. The boxed portion of
30 the sequence indicates the HDAC domain.

FIGS. 1D-1G show the cDNA sequence of *HDAC9a* (SEQ ID NO: 3). The arrows and numbers in the *HDAC9a* sequence indicate exons. The boxed portion of the sequence indicates the HDAC domain.

FIGS. 1H-1I show the cDNA sequence of *HDRP(ΔNLS)* (SEQ ID NO:9).

5 FIGS. 1J-1L show the cDNA sequence of *HDAC9(ΔNLS)* (SEQ ID NO:5).

FIGS. 1M-1O show the cDNA sequence of *HDAC9a(ΔNLS)* (SEQ ID NO:7).

FIG. 2 is a schematic representation of the order in which FIGS. 2A-2E should be viewed.

10 FIG. 2A shows the amino acid sequence of HDAC9 (SEQ ID NO: 2).

FIG. 2B shows the amino acid sequence of HDAC9a (SEQ ID NO: 4).

FIG. 2C shows the amino acid sequence of HDAC9(ΔNLS) (SEQ ID NO: 6).

FIG. 2D shows the amino acid sequence of HDAC9a(ΔNLS) (SEQ ID NO: 8).

15 FIG. 2E shows the amino acid sequence of and HDRP(ΔNLS) (SEQ ID NO: 10).

FIG. 3 is a schematic representation of the order in which FIGS. 3A-3C should be viewed.

20 FIGS. 3A-3C show an amino acid sequence alignment of HDRP (SEQ ID NO: 11), HDAC9 (SEQ ID NO: 2), HDAC9a (SEQ ID NO: 4), and HDAC4 (SEQ ID NO: 12) polypeptides. Amino acid sequences of HDAC9 (GenBank Accession: AY032737; SEQ ID NO: 2) and HDAC9a (GenBank Accession: AY032738; SEQ ID NO: 4) are aligned with HDRP (GenBank Accession: BAA34464; SEQ ID NO: 11) and HDAC4 (GenBank Accession: NP_006028; SEQ ID NO: 12). The identical residues in all proteins are boxed with solid lines. The similar residues are boxed with dotted lines.

25 FIG. 4 shows a schematic representation of the human *HDAC9* gene structure. The striped boxes represent exons present in isoforms HDRP, HDAC9a, and HDAC9. The lines represent introns. Broken lines are used for larger introns (with size in base pair on top). The 5' untranslated region cDNA and coding region cDNA are represented here. Exons 1-12 encode a non-catalytic domain of the

30

polypeptides, and exons 14-21 encode the histone deacetylase catalytic domain of the polypeptides, which provide the polypeptides with deacetylase activity.

FIG. 5 is a schematic representation of the order in which FIGS. 5A-5D should be viewed.

5 FIGS. 5A-5D show the nucleic acid sequence of *HDAC9*, containing all exons expressed in the various isoforms of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* of the present invention (SEQ ID NO:13).

FIG. 6A is a scanned image of a multiple human tissue Northern blot that was probed to determine mRNA expression of *HDAC9* using a cDNA probe that
10 recognizes both *HDAC9* and *HDAC9a*. The tissues examined are lane 1, heart; lane 2, brain; lane 3, placenta; lane 4, lung; lane 5, liver; lane 6, skeletal muscle; lane 7, kidney; and lane 8, pancreas. Positions of the RNA size marker in kilobases (kb) are indicated to the left of the blot.

FIG. 6B is a scanned image of an electrophoretic gel showing the results of
15 RT-PCR analyses of mRNA from the same tissues as examined in the Northern blot of FIG. 6A to determine the distribution of *HDAC9* and *HDAC9a* mRNA among these tissues. PCR products were resolved by agarose gel electrophoresis and visualized by ethidium bromide under UV light. A 1-kb DNA ladder was run on both sides of the gel with the size (in kb) indicated on the left. On the right side, the
20 expected products for *HDAC9* and *HDAC9a* are indicated as 9 and 9a, respectively.

FIG. 7 is a graph of HDAC enzymatic activity of HDAC anti-FLAG-immunoprecipitated proteins isolated from vector control, HDAC9-FLAG, and HDAC9a-FLAG transfected 293T cells, as measured in fluorescence units using *FLUOR DE LYST*[™] as a substrate in the presence or absence of 1 μM TSA. Results
25 are shown as the mean of three independent assays. The inset is a scanned image of an anti-FLAG Western blot showing the amount of proteins used in the assay. V, Vector control; 9, HDAC9-FLAG; and 9a, HDAC9a-FLAG.

FIG. 8 is a graph of HDAC enzymatic activity of HDAC anti-FLAG-immunoprecipitated proteins isolated from vector control, and HDAC9a-FLAG
30 (treated with 2 μM SAHA or left untreated) transfected 293T cells, as measured by ³H-acetic acid released from ³H-histones in the presence or absence of 2 μM SAHA.

Vector control; HDAC9a, HDAC9a-FLAG; and HDAC9a+, HDAC9a-FLAG + SAHA.

FIG. 9A shows a scanned image of a Western blot of 293T whole cell lysate and anti-FLAG immunoprecipitates from 293T cells transfected with vector, HDAC9-FLAG or HDAC9a-FLAG using antibodies against MEF2 and FLAG. Top panel, anti-MEF2 Western; bottom panel, anti-FLAG Western. L, 293T whole cell lysate; V, vector control IP; 9, HDAC9-FLAG IP; 9a, HDAC9a-FLAG IP.

FIG. 9B is a graph showing the transcription level of p3XMEF2-*Luc* in the presence or absence of pcDNA3 empty vector (-), pCMV-MEF2C, and/or a vector encoding pFLAG-HDAC9 or pFLAG-HDAC9a. p3XMEF2-*Luc* (100 ng) and pRL-TK (5 ng) were transfected into 293T cells with pcDNA3 empty vector (-) or with pCMV-MEF2C (100 ng) (+) along with the indicated amount of pFLAG-HDAC9 or pFLAG-HDAC9a. pFLAG empty vector was used to adjust the DNA to an equal amount in each transfection. The firefly luciferase activity was first normalized to the co-transfected Renilla luciferase activity and the value for MEF2C alone was then set as 1. Results are shown as the mean of three independent transfections +/- standard deviation.

FIG. 10 shows a schematic representation of the HDAC domains of human non-Sir2 family HDACs and HDRP. The boxes represent histone deacetylase (HDAC) domains.

FIG. 11 is a schematic representation of the order in which FIGS. 11A-11F should be viewed.

FIGS. 11A-11F show the nucleotide sequence of the vector pFLAG-CMV-5b-HDAC9 (VR1) (SEQ ID NO: 14). Lowercase letters are vector backbone, uppercase letters are HDAC9 sequence. "Acc" was added at the beginning of the HDAC9 sequence for translation initiation.

FIG. 12 is a schematic representation of the order in which FIGS. 12-1 through 12-66 should be viewed.

FIGS. 12-1 through 12-66 show the nucleotide sequence of the vector pFLAG-CMV-5b-HDAC9a (VR2), with restriction enzyme sites indicated (SEQ ID NO: 14).

FIG. 13 is a schematic representation of the order in which FIGS. 13A-13E should be viewed.

FIGS. 13A-13E show the nucleotide sequence of the vector pFLAG-CMV-5b-HDAC9a (VR2) (SEQ ID NO: 15). Lowercase letters are vector backbone,
5 uppercase letters are HDAC9a sequence. "Acc" was added at the beginning of the HDAC9a sequence for translation initiation.

FIG. 14 is a schematic representation of the order in which FIGS. 14-1 through 14-61 should be viewed.

FIGS. 14-1 through 14-61 show the nucleotide sequence of the vector
10 pFLAG-CMV-5b-HDAC9a (VR2), with restriction enzyme sites indicated (SEQ ID NO: 15).

DETAILED DESCRIPTION OF THE INVENTION

A protein designated HDRP (See Zhou *et al.*, Proc. Natl. Acad. Sci. USA,
15 97:1056-1061 (2000)) (also called MITR (See Sparrow *et al.*, EMBO J. 18:5085-5098(1999); Zhang *et al.*, J. Biol. Chem., 276:35-39 (2001); and Zhang *et al.*, Proc. Natl. Acad. Sci. USA, 98:7354-7359 (2001)) that is 50% identical to the N-terminal domains of histone deacetylase 4 (HDAC4) and histone deacetylase 5 (HDAC5) was recently identified. The cloning and characterization of a novel histone deacetylase,
20 *HDAC9*, of which HDRP is an alternatively spliced isoform is described herein. The cDNA sequence of *HDAC9* is shown in FIGS. 1A-1C (SEQ ID NO: 1), and the HDAC9 amino acid sequence is shown in FIG. 2A (SEQ ID NO: 2). In addition to cloning *HDAC9*, other alternatively spliced isoforms of HDAC9, designated as HDAC9a (a polypeptide that is 132 amino acids shorter at the C-terminal end than
25 HDAC9), and isoforms of HDAC9, HDAC9a, and HDRP polypeptides that lack the nuclear localization signal (NLS) in the N-terminal non-catalytic end of HDAC9, termed HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS), respectively were also identified. The cDNA sequence of *HDAC9a* is shown in FIGS. 1D-1G (SEQ ID NO: 3), and the HDAC9a amino acid sequence is shown in FIG. 2B (SEQ ID
30 NO: 4). The cDNA sequence of *HDAC9* lacking amino acids encoding an NLS (*HDAC9*(Δ NLS)) is shown in FIGS. 1J-1L (SEQ ID NO: 5), and the HDAC9 lacking an NLS amino acid sequence is shown in FIG. 2C (SEQ ID NO: 6). The cDNA

sequence of *HDAC9a* encoding a polypeptide lacking an NLS (*HDAC9a*(Δ NLS)) is shown in FIGS. 1M-1O (SEQ ID NO: 7), and the *HDAC9a* lacking an NLS amino acid sequence is shown in FIG. 2D (SEQ ID NO: 8). The cDNA sequence of *HDRP* encoding a polypeptide lacking an NLS (*HDRP*(Δ NLS)) is shown in FIGS. 1H-1I (SEQ ID NO: 9), and the *HDRP* lacking an NLS amino acid sequence is shown in FIG. 2E (SEQ ID NO: 10).

POLYPEPTIDES OF THE INVENTION

The present invention features isolated or recombinant HDAC9 polypeptides, HDAC9a polypeptides, HDAC9(Δ NLS) polypeptides, HDAC9a(Δ NLS) polypeptides, and HDRP(Δ NLS) polypeptides, and fragments, derivatives, and variants thereof, as well as polypeptides encoded by nucleotide sequences described herein (*e.g.*, other variants). As used herein, the term "polypeptide" refers to a polymer of amino acids, and not to a specific length; thus, peptides, oligopeptides, and proteins are included within the definition of a polypeptide.

As used herein, a polypeptide is said to be "isolated," "substantially pure," or "substantially pure and isolated" when it is substantially free of cellular material, when it is isolated from recombinant or non-recombinant cells, or free of chemical precursors or other chemicals when it is chemically synthesized. Typically, the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide is isolated, substantially pure, or substantially pure and isolated when it has a relative increased concentration or activity of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS), in comparison to total HDAC concentration or activity. Preferably the increased activity or concentration of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) is at least 2-fold, more preferably, at least 5-fold, and most preferably, at least 10 fold, in comparison to total HDAC concentration or activity. In addition, a polypeptide can be joined to another polypeptide with which it is not normally associated in a cell (*e.g.*, in a "fusion protein") and still be "isolated," "substantially pure," or "substantially pure and isolated." An isolated, substantially pure, or substantially pure and isolated polypeptide may be obtained, for example, using affinity

purification techniques described herein, as well as other techniques described herein and known to those skilled in the art.

By a "histone deacetylase polypeptide" is meant a polypeptide having histone deacetylase activity, transcription repression activity, and/or the ability to deacetylate other substrates, for example, transcription factors, including p53, CoRest, E2F, GATA-1, TFIIe, and TFIIIF that normally have a nuclear or cytoplasmic location in a cell. A histone deacetylase polypeptide is also a polypeptide whose activity can be inhibited by molecules having HDAC inhibitory activity. These molecules fall into four general classes: 1) short-chain fatty acids (e.g., 4-phenylbutyrate and valproic acid); 2) hydroxamic acids(e.g. SAHA, Pyroxamide, trichostatin A (TSA), oxamflatin and CHAPs, such as, CHAP1 and CHAP 31); 3) cyclic tetrapeptides (Trapoxin A, Apicidin and Depsipeptide (FK-228, also known as FR9011228); 4) benzamides (e.g., MS-275); and other compounds such as Scriptaid. Examples of such compounds can be found in U.S. Patent Nos. 5,369,108, issued on November 29, 1994, 5,700,811, issued on December 23, 1997, and 5,773,474, issued on June 30, 1998 to Breslow *et al.*, U.S. Patent Nos. 5,055,608, issued on October 8, 1991, and 5,175,191, issued on December 29, 1992 to Marks *et al.*, as well as, Yoshida *et al.*, Bioessays 17, 423-430 (1995), Saito *et al.*, PNAS USA 96, 4592-4597, (1999), Furamai *et al.*, PNAS USA 98 (1), 87-92 (2001), Komatsu *et al.*, Cancer Res. 61(11), 4459-4466 (2001), Su *et al.*, Cancer Res. 60, 3137-3142 (2000), Lee *et al.*, Cancer Res. 61(3), 931-934 and Suzuki *et al.* J. Med. Chem. 42(15), 3001-3003 (1999) the entire content of all of which are hereby incorporated by reference. Examples of such histone deacetylase polypeptides include HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), HDRP(Δ NLS); a substantially pure polypeptide comprising SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; and a polypeptide having preferably at least 60%, more preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to any one of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10, as determined using the BLAST program and parameters described herein.

In one embodiment, the histone deacetylase polypeptide has histone deacetylase activity, transcription repression activity, the ability to deacetylate substrates, or is inhibited by trichostatin A or a hybrid polar compound such as

SAHA. In another embodiment, the HDAC9(Δ NLS) polypeptide has any two of the above biological activities. In still another embodiment, the HDAC9(Δ NLS) polypeptide has any three of the above biological activities. In yet another embodiment, the HDAC9(Δ NLS) polypeptide has all of the above biological activities.

5 An HDAC9 polypeptide is a histone deacetylase polypeptide as described above. An HDAC9 polypeptide preferably has at least 60%, more preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to SEQ ID NO: 2, as determined using the BLAST program and parameters described herein.

10 An HDAC9 polypeptide is also a polypeptide that comprises the amino acids encoded by exons 23, 24, 25 and/or 26, and that does not comprise the amino acids encoded by exon 13 of the *HDAC9* nucleic acid sequence, as shown in FIGS. 1A-1C, FIG. 4, and FIGS. 5A-5D. Preferably, an HDAC9 polypeptide comprises the sequence of SEQ ID NO: 2. More preferably, an HDAC9 polypeptide consists of

15 the sequence of SEQ ID NO: 2. An HDAC polypeptide is also a polypeptide comprising the amino acid sequence of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 1.

An HDAC9a polypeptide is a histone deacetylase polypeptide as described above. An HDAC9a polypeptide preferably has at least 60%, more preferably, 70%,

20 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to SEQ ID NO: 4, as determined using the BLAST program and parameters described herein. An HDAC9a polypeptide is also a polypeptide that comprises the amino acids encoded by exon 22, and that does not comprise the amino acids encoded by exons 13, 23, 24, 25, or 26 of the *HDAC9* nucleic acid sequence, as shown in FIGS. 1D-

25 1G, FIG. 4, and FIGS. 5A-5D. Preferably, an HDAC9a polypeptide comprises the sequence of SEQ ID NO: 4. More preferably, an HDAC9a polypeptide consists of the sequence of SEQ ID NO: 4. An HDAC9a polypeptide is also a polypeptide comprising the amino acid sequence of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 3.

30 An HDAC9(Δ NLS) is a histone deacetylase polypeptide as described above. An HDAC9(Δ NLS) polypeptide does not comprise a nuclear localization signal (NLS). An HDAC9(Δ NLS) polypeptide preferably has at least 60%, more

preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to SEQ ID NO: 6, as determined using the BLAST program and parameters described herein. An HDAC9(Δ NLS) polypeptide is also a polypeptide that comprises the amino acids encoded by exons 23, 24, 25, and/or 26, and that does not
5 comprise the amino acids encoded by exons 7 or 13 of the *HDAC9* nucleic acid sequence, as shown in FIGS. 1J-1L, and FIGS. 5A-5D. Preferably, an HDAC9(Δ NLS) polypeptide comprises the sequence of SEQ ID NO: 6. More preferably, an HDAC9(Δ NLS) polypeptide consists of the sequence of SEQ ID NO: 6. An HDAC9(Δ NLS) polypeptide is also a polypeptide comprising the amino acid
10 sequence of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 5.

An HDAC9a(Δ NLS) polypeptide is a histone deacetylase polypeptide as described above. An HDAC9a(Δ NLS) does not comprise a nuclear localization signal (NLS). An HDAC9a(Δ NLS) polypeptide preferably has at least 60%, more preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence
15 identity to SEQ ID NO: 8, as determined using the BLAST program and parameters described herein. An HDAC9a(Δ NLS) polypeptide is also a polypeptide that comprises the amino acids encoded by exon 22, and that does not comprise the amino acids encoded by exons 7, 13, 23, 24, 25, or 26 of the *HDAC9* nucleic acid sequence, as shown in FIGS. 1M-1O, and FIGS. 5A-5D. Preferably, an
20 HDAC9a(Δ NLS) polypeptide comprises the sequence of SEQ ID NO: 8. More preferably, an HDAC9a(Δ NLS) polypeptide consists of the sequence of SEQ ID NO: 8. An HDAC9a(Δ NLS) polypeptide is also a polypeptide comprising the amino acid sequence of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 7.

An HDRP(Δ NLS) polypeptide is a histone deacetylase polypeptide as
25 described above. An HDRP(Δ NLS) does not comprise a nuclear localization signal (NLS). An HDRP(Δ NLS) polypeptide preferably has at least 60%, more preferably, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% sequence identity to SEQ ID NO: 10, as determined using the BLAST program and parameters described herein. An HDRP(Δ NLS) polypeptide is also a polypeptide that does not comprise
30 the amino acids encoded by exons 7 or 13-26 of the *HDAC9* nucleic acid sequence, as shown in FIGS. 1H-1I and FIGS. 5A-5D. Preferably, an HDRP(Δ NLS) polypeptide comprises the sequence of SEQ ID NO: 10. More preferably, an

HDRP(ANLS) polypeptide consists of the sequence of SEQ ID NO: 10. An HDRP(ANLS) polypeptide is also a polypeptide comprising the amino acid sequence of the polypeptide encoded by the nucleic acid sequence of SEQ ID NO: 9.

The polypeptides of the invention can be purified to homogeneity. It is understood, however, that preparations in which the polypeptide is not purified to homogeneity are useful. The critical feature is that the preparation allows for the desired function of the polypeptide, even in the presence of considerable amounts of other components. Thus, the invention encompasses various degrees of purity. In one embodiment, the language "substantially free of cellular material" includes preparations of the polypeptide having less than about 30% (by dry weight) other proteins (*i.e.*, contaminating protein), less than about 20% other proteins, less than about 10% other proteins, or less than about 5% other proteins.

When a polypeptide is recombinantly produced, it can also be substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, less than about 10%, or less than about 5% of the volume of the polypeptide preparation. The language "substantially free of chemical precursors or other chemicals" includes preparations of the polypeptide in which it is separated from chemical precursors or other chemicals that are involved in its synthesis. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of the polypeptide having less than about 30% (by dry weight) chemical precursors or other chemicals, less than about 20% chemical precursors or other chemicals, less than about 10% chemical precursors or other chemicals, or less than about 5% chemical precursors or other chemicals.

In one embodiment, a polypeptide of the invention comprises an amino acid sequence encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and complements and portions thereof, (*e.g.*, a complement of any one of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9 or a portion of any one of SEQ ID NO: 1 or SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9).

The polypeptides of the invention also encompass fragments and sequence variants. Variants include a substantially homologous polypeptide encoded by the

- same genetic locus in an organism, *i.e.*, an allelic variant, as well as other variants. Variants also encompass polypeptides derived from other genetic loci in an organism, but having substantial homology to a polypeptide encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and complements and portions thereof, or having substantial homology to a polypeptide encoded by a nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of nucleotide sequences encoding any one of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10.
- 10 Variants also include polypeptides substantially homologous or identical to these polypeptides but derived from another organism, *i.e.*, an ortholog. Variants also include polypeptides that are substantially homologous or identical to these polypeptides that are produced by chemical synthesis. Variants also include polypeptides that are substantially homologous or identical to these polypeptides that
- 15 are produced by recombinant methods.

- As used herein, two polypeptides (or a region of the polypeptides) are substantially homologous or identical when the amino acid sequences are at least about 60-65%, typically at least about 70-75%, more typically at least about 80-85%, and most typically greater than about 90-95% or more homologous or identical. A
- 20 substantially identical or homologous amino acid sequence, according to the present invention, will be encoded by a nucleic acid molecule hybridizing to SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or a portion thereof, under stringent conditions as more particularly described herein, or will be encoded by a nucleic acid molecule hybridizing to a nucleic acid sequence encoding SEQ ID
- 25 NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or portion thereof, under stringent conditions as more particularly described herein.

- The percent identity of two nucleotide or amino acid sequences can be determined by aligning the sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first sequence). The nucleotides or amino
- 30 acids at corresponding positions are then compared, and the percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = # of identical positions/total # of positions x 100). In

certain embodiments, the length of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS) amino acid or nucleotide sequence aligned for comparison purposes is at least 30%, preferably, at least 40%, more preferably, at least 60%, and even more preferably, at least 70%, 80%, 90%, or 100% of the length of the reference sequence, for example, those sequences provided in FIGS. 1A-1O and 2A-2E. The actual comparison of the two sequences can be accomplished by well-known methods, for example, using a mathematical algorithm. A preferred, non-limiting example of such a mathematical algorithm is described in Karlin *et al.*, Proc. Natl. Acad. Sci. USA, 90:5873-5877 (1993). Such an algorithm is incorporated into the BLASTN and BLASTX programs (version 2.2) as described in Schaffer *et al.*, Nucleic Acids Res., 29:2994-3005 (2001). When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, BLASTN) can be used. See <http://www.ncbi.nlm.nih.gov>, as available on August 10, 2001. In one embodiment, the database searched is a non-redundant (NR) database, and parameters for sequence comparison can be set at: no filters; Expect value of 10; Word Size of 3; the Matrix is BLOSUM62; and Gap Costs have an Existence of 11 and an Extension of 1.

Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, CABIOS (1989). Such an algorithm is incorporated into the ALIGN program (version 2.0), which is part of the GCG (Accelrys) sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Additional algorithms for sequence analysis are known in the art and include ADVANCE and ADAM as described in Torellis and Robotti, Comput. Appl. Biosci., 10: 3-5 (1994); and FASTA described in Pearson and Lipman, Proc. Natl. Acad. Sci USA, 85: 2444-8 (1988).

In another embodiment, the percent identity between two amino acid sequences can be accomplished using the GAP program in the GCG software package (available at <http://www.accelrys.com>, as available on August 31, 2001) using either a Blossom 63 matrix or a PAM250 matrix, and a gap weight of 12, 10, 8, 6, or 4 and a length weight of 2, 3, or 4. In yet another embodiment, the percent

identity between two nucleic acid sequences can be accomplished using the GAP program in the GCG software package (available at <http://www.cgc.com>), using a gap weight of 50 and a length weight of 3.

The invention also encompasses HDAC9, HDAC9a, HDAC9(Δ NLS),
5 HDAC9a Δ NLS, and HDRP(Δ NLS) polypeptides having a lower degree of identity but having sufficient similarity so as to perform one or more of the same functions performed by an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a Δ NLS, or HDRP(Δ NLS) polypeptide encoded by a nucleic acid molecule of the invention. Similarity is determined by conserved amino acid substitution. Such substitutions
10 are those that substitute a given amino acid in a polypeptide by another amino acid of like characteristics. Conservative substitutions are likely to be phenotypically silent. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu, and Ile; interchange of the hydroxyl residues Ser and Thr; exchange of the acidic residues Asp and Glu;
15 substitution between the amide residues Asn and Gln; exchange of the basic residues Lys and Arg; and replacements among the aromatic residues Phe and Tyr. Guidance concerning which amino acid changes are likely to be phenotypically silent are found in Bowie *et al.*, Science 247: 1306-1310 (1990).

A variant polypeptide can differ in amino acid sequence by one or more
20 substitutions, deletions, insertions, inversions, fusions, and truncations or a combination of any of these. Further, variant polypeptides can be fully functional or can lack function in one or more activities, for example, in histone deacetylase activity or transcription repression activity. Fully functional variants typically contain only conservative variation or variation in non-critical residues or in
25 non-critical regions. Functional variants can also contain substitution of similar amino acids that result in no change or an insignificant change in function. Alternatively, such substitutions may positively or negatively affect function to some degree. Non-functional variants typically contain one or more non-conservative amino acid substitutions, deletions, insertions, inversions, or truncations or a
30 substitution, insertion, inversion, or deletion in a critical residue or critical region, such critical regions include the HDAC domains, which provide the polypeptide

with deacetylase activity, as shown in the nucleic acid sequences of FIGS. 1A-1G, as well as in the schematic of FIG. 4.

Amino acids that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham *et al.*, Science, 244: 1081-1085 (1989)). The latter procedure introduces a single alanine mutation at each of the residues in the molecule (one mutation per molecule). The resulting mutant molecules are then tested for biological activity *in vitro*. Sites that are critical for polypeptide activity can also be determined by structural analysis, such as crystallization, nuclear magnetic resonance, or photoaffinity labeling (See Smith *et al.*, J. Mol. Biol., 224: 899-904 (1992); and de Vos *et al.* Science, 255: 306-312 (1992)).

The invention also includes HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS) polypeptide fragments of the polypeptides of the invention. Fragments can be derived from a polypeptide comprising SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10, or from a polypeptide encoded by a nucleic acid molecule comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9 or a portion thereof and the complements thereof or other variants. The present invention also encompasses fragments of the variants of the polypeptides described herein. Useful fragments include those that retain one or more of the biological activities of the polypeptide as well as fragments that can be used as an immunogen to generate polypeptide-specific antibodies.

Biologically active fragments (peptides that are, for example, 6, 9, 12, 15, 16, 20, 30, 35, 36, 37, 38, 39, 40, 50, 100, or more amino acids in length) can comprise a domain, segment, or motif, for example, an HDAC domain, that has been identified by analysis of the polypeptide sequence using well-known methods, *e.g.*, signal peptides, extracellular domains, one or more transmembrane segments or loops, ligand binding regions, zinc finger domains, DNA binding domains, acylation sites, glycosylation sites, or phosphorylation sites.

Fragments can be discrete (not fused to other amino acids or polypeptides) or can be within a larger polypeptide. Further, several fragments can be comprised within a single larger polypeptide. In one embodiment a fragment designed for

expression in a host can have heterologous pre- and pro-polypeptide regions fused to the amino terminus of the polypeptide fragment and an additional region fused to the carboxyl terminus of the fragment.

The invention thus provides chimeric or fusion polypeptides. These
5 comprise an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a Δ NLS, or HDRP(Δ NLS) polypeptide of the invention operatively linked to a heterologous protein or polypeptide having an amino acid sequence not substantially homologous to the polypeptide. "Operatively linked" indicates that the polypeptide and the heterologous protein are fused in-frame. The heterologous protein can be fused to
10 the N-terminus or C-terminus of the polypeptide. In one embodiment, the fusion polypeptide does not affect the function of the polypeptide per se. For example, the fusion polypeptide can be a GST-fusion polypeptide in which the polypeptide sequences are fused to the C-terminus of the GST sequences. Other types of fusion polypeptides include, but are not limited to, enzymatic fusion polypeptides, for
15 example, β -galactosidase fusions, yeast two-hybrid GAL fusions, poly-His fusions, and Ig fusions. Such fusion polypeptides, particularly poly-His fusions, can facilitate the purification of recombinant polypeptide. In certain host cells (*e.g.*, mammalian host cells), expression and/or secretion of a polypeptide can be increased by using a heterologous signal sequence. Therefore, in another
20 embodiment, the fusion polypeptide contains a heterologous signal sequence at its N-terminus.

EP-A 0464 533 discloses fusion proteins comprising various portions of immunoglobulin constant regions. The Fc is useful in therapy and diagnosis and thus results, for example, in improved pharmacokinetic properties (EP-A 0232 262).
25 In drug discovery, for example, human proteins have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists. (See Bennett *et al.*, *Journal of Molecular Recognition*, 8: 52-58 (1995) and Johanson *et al.*, *The Journal of Biological Chemistry*, 270,16: 9459-9471 (1995)). Thus, this invention also encompasses soluble fusion polypeptides containing a polypeptide of
30 the invention and various portions of the constant regions of heavy or light chains of immunoglobulins of various subclass (IgG, IgM, IgA, IgE).

A chimeric or fusion polypeptide can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques.

In another embodiment, the fusion gene can be synthesized by conventional

- 5 techniques including automated DNA synthesizers. Alternatively, PCR amplification of nucleic acid fragments can be carried out using anchor primers that give rise to complementary overhangs between two consecutive nucleic acid fragments that can subsequently be annealed and re-amplified to generate a chimeric nucleic acid sequence (see Ausubel *et al.*, "Current Protocols in Molecular Biology,"
10 John Wiley & Sons, (1998), the entire teachings of which are incorporated by reference herein). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST protein). A nucleic acid molecule encoding a polypeptide of the invention can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the polypeptide.

- 15 The substantially pure, isolated, or substantially pure and isolated HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a Δ NLS, or HDRP(Δ NLS) polypeptide can be purified from cells that naturally express it, purified from cells that have been altered to express it (recombinant), or synthesized using known protein synthesis methods. In one embodiment, the polypeptide is produced by recombinant DNA techniques.
20 For example, a nucleic acid molecule encoding the polypeptide is cloned into an expression vector, the expression vector introduced into a host cell, and the polypeptide expressed in the host cell. The polypeptide can then be isolated from the cells by an appropriate purification scheme using standard protein purification techniques.

- 25 In general, HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a Δ NLS, and HDRP(Δ NLS) polypeptides of the present invention can be used as a molecular weight marker on SDS-PAGE gels or on molecular sieve gel filtration columns using art-recognized methods. The polypeptides of the present invention can be used to raise antibodies or to elicit an immune response. The polypeptides can also
30 be used as a reagent, *e.g.*, a labeled reagent, in assays to quantitatively determine levels of the polypeptide or a molecule to which it binds (*e.g.*, a receptor or a ligand) in biological fluids. The polypeptides can also be used as markers for cells or tissues

in which the corresponding polypeptide is preferentially expressed, either constitutively, during tissue differentiation, or in a diseased state. The polypeptides can be used to isolate a corresponding binding agent, and to screen for peptide or small molecule antagonists or agonists of the binding interaction. The polypeptides
5 of the present invention can also be used as therapeutic agents.

NUCLEIC ACID MOLECULES OF THE INVENTION

The present invention also features isolated *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid molecules.

10 By a "histone deacetylase nucleic acid molecule" is meant a nucleic acid molecule that encodes a histone deacetylase polypeptide. Such histone nucleic acids include, for example, the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule described in detail herein; an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or
15 SEQ ID NO: 9; a complement of an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9; an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2,
20 SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; a nucleic acid that is hybridizable under high stringency conditions to a nucleic acid molecule that encodes any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, or SEQ ID NO: 8, or a complement thereof; a nucleic acid molecule that is hybridizable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3,
25 SEQ ID NO: 5, or SEQ ID NO: 7; and an isolated nucleic acid molecule that has at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with any one of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or a complement thereof.

An *HDAC9* nucleic acid molecule is a nucleic acid molecule that encodes an
30 *HDAC9* polypeptide. In one embodiment, the *HDAC9* nucleic acid molecule is selected from: a nucleic acid molecule that comprises the nucleic acid sequence of SEQ ID NO: 1; a complement of an isolated nucleic acid comprising SEQ ID NO: 1;

an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2; a nucleic acid that is hybridizable under high stringency conditions to a nucleic acid molecule that encodes SEQ ID NO: 2; a
5 nucleic acid molecule that is hybridizable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 1; and an isolated nucleic acid molecule that has preferably, at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with SEQ ID NO: 1, as determined using the BLAST program and parameters described herein. In another
10 embodiment, the *HDAC9* nucleic acid molecule consists of the nucleic acid sequence of SEQ ID NO: 1.

An *HDAC9a* nucleic acid molecule is a nucleic acid molecule that encodes an *HDAC9a* polypeptide. An *HDAC9a* nucleic acid molecule preferably has at least 55%, sequence identity to SEQ ID NO: 3. In one embodiment, the *HDAC9a* nucleic
15 acid molecule is selected from: a nucleic acid molecule that comprises the nucleic acid sequence of SEQ ID NO: 3; a complement of an isolated nucleic acid comprising SEQ ID NO: 3; an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 4; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 4; a nucleic acid that is
20 hybridizable under high stringency conditions to a nucleic acid molecule that encodes SEQ ID NO: 4; a nucleic acid molecule that is hybridizable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 3; and an isolated nucleic acid molecule that has preferably, at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity
25 with SEQ ID NO: 3 or a complement thereof, as determined using the BLAST program and parameters described herein. In another embodiment, the *HDAC9a* nucleic acid molecule consists of the nucleic acid sequence of SEQ ID NO: 3.

An *HDAC9(ΔNLS)* nucleic acid molecule is a nucleic acid molecule that encodes an *HDAC9(ΔNLS)* polypeptide. In one embodiment, the *HDAC9(ΔNLS)*
30 nucleic acid molecule is selected from: a nucleic acid molecule that comprises the nucleic acid sequence of SEQ ID NO: 5; a complement of an isolated nucleic acid comprising SEQ ID NO: 5; an isolated nucleic acid encoding a histone deacetylase

polypeptide of SEQ ID NO: 6; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 6; a nucleic acid that is hybridizeable under high stringency conditions to a nucleic acid molecule that encodes SEQ ID NO: 6; a nucleic acid molecule that is hybridizeable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 5; and an isolated nucleic acid molecule that has preferably, at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with SEQ ID NO: 5 or a complement thereof, as determined using the BLAST program and parameters described herein. In another embodiment, the

10 *HDAC9(ΔNLS)* nucleic acid molecule consists of the nucleic acid sequence of SEQ ID NO: 5.

An *HDAC9a(ΔNLS)* nucleic acid molecule is a nucleic acid molecule that encodes an *HDAC9a(ΔNLS)* polypeptide. In one embodiment, the *HDAC9a(ΔNLS)* nucleic acid molecule is selected from: a nucleic acid molecule that comprises the

15 nucleic acid sequence of SEQ ID NO: 7; a complement of an isolated nucleic acid comprising SEQ ID NO: 7; an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 8; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 8; a nucleic acid that is hybridizeable under high stringency conditions to a nucleic acid molecule that

20 encodes SEQ ID NO: 8; a nucleic acid molecule that is hybridizeable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 7; and an isolated nucleic acid molecule that has preferably, at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with SEQ ID NO: 7 or a complement thereof, as determined using the BLAST

25 program and parameters described herein. In another embodiment, the *HDAC9a(ΔNLS)* nucleic acid molecule consists of the nucleic acid sequence of SEQ ID NO: 7.

An "*HDRP(ΔNLS)* nucleic acid molecule" is a nucleic acid molecule that encodes an *HDRP(ΔNLS)* polypeptide. In one embodiment, the *HDRP(ΔNLS)*

30 nucleic acid molecule is selected from: a nucleic acid molecule that comprises the nucleic acid sequence of SEQ ID NO: 9; a complement of an isolated nucleic acid comprising SEQ ID NO: 9; an isolated nucleic acid encoding a histone deacetylase

polypeptide of SEQ ID NO: 10; a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 10; and an isolated nucleic acid molecule that has preferably, at least 55%, more preferably, 60%, 65%, 70%, 75%, 80%, 85%, or 90%, and most preferably, 95% or 99% sequence identity with SEQ ID NO: 9 or a complement thereof, as determined using the BLAST program and parameters described herein.. In another embodiment, the *HDRP(Δ NLS)* nucleic acid molecule consists of the nucleic acid sequence of SEQ ID NO: 9.

The isolated nucleic acid molecules of the present invention can be RNA, for example, mRNA, or DNA, such as cDNA and genomic DNA. DNA molecules can be double-stranded or single-stranded; single stranded RNA or DNA can be either the coding, or sense, strand or the non-coding, or antisense, strand. The nucleic acid molecule can include all or a portion of the coding sequence of the gene and can further comprise additional non-coding sequences such as introns and non-coding 3' and 5' sequences (including regulatory sequences, for example). Additionally, the nucleic acid molecule can be fused to a marker sequence, for example, a sequence that encodes a polypeptide to assist in isolation or purification of the polypeptide. Such sequences include, but are not limited to, those that encode a glutathione-S-transferase (GST) fusion protein and those that encode a hemagglutinin A (HA) polypeptide marker from influenza.

An "isolated," "substantially pure," or "substantially pure and isolated" nucleic acid molecule, as used herein, is one that is separated from nucleic acids that normally flank the gene or nucleotide sequence (as in genomic sequences) and/or has been completely or partially purified from other transcribed sequences (e.g., as in an RNA or cDNA library). For example, an isolated nucleic acid of the invention may be substantially isolated with respect to the complex cellular milieu in which it naturally occurs, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized. In some instances, the isolated material will form part of a composition (for example, a crude extract containing other substances), buffer system, or reagent mix. In other circumstances, the material may be purified to essential homogeneity, for example, as determined by agarose gel electrophoresis or column chromatography such as

HPLC. Preferably, an isolated nucleic acid molecule comprises at least about 50, 80, or 90% (on a molar basis) of all macromolecular species present.

With regard to genomic DNA, the term "isolated" also can refer to nucleic acid molecules that are separated from the chromosome with which the genomic DNA is naturally associated. For example, the isolated nucleic acid molecule can contain less than about 5 kb, 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb, or 0.1 kb of nucleotides that flank the nucleic acid molecule in the genomic DNA of the cell from which the nucleic acid molecule is derived.

The *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule can be fused to other coding or regulatory sequences and still be considered isolated. Thus, recombinant DNA contained in a vector is included in the definition of "isolated" as used herein. Also, isolated nucleic acid molecules include recombinant DNA molecules in heterologous host cells, as well as partially or substantially purified DNA molecules in solution. "Isolated" nucleic acid molecules also encompass *in vivo* and *in vitro* RNA transcripts of the DNA molecules of the present invention. An isolated nucleic acid molecule or nucleotide sequence can include a nucleic acid molecule or nucleotide sequence that is synthesized chemically or by recombinant means. Therefore, recombinant DNA contained in a vector are included in the definition of "isolated" as used herein.

Isolated nucleotide molecules also include recombinant DNA molecules in heterologous organisms, as well as partially or substantially purified DNA molecules in solution. *In vivo* and *in vitro* RNA transcripts of the DNA molecules of the present invention are also encompassed by "isolated" nucleotide sequences. Such isolated nucleotide sequences are useful in the manufacture of the encoded polypeptide, as probes for isolating homologous sequences (*e.g.*, from other mammalian species), for gene mapping (*e.g.*, by *in situ* hybridization with chromosomes), or for detecting expression of the gene in tissue (*e.g.*, human tissue), such as by Northern blot analysis.

The present invention also pertains to variant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid molecules that are not necessarily found in nature but that encode an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide. Thus, for

example, DNA molecules that comprise a sequence that is different from the naturally-occurring *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleotide sequence but which, due to the degeneracy of the genetic code, encode an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or
5 *HDRP(ΔNLS)* polypeptide of the present invention are also the subject of this invention.

The invention also encompasses *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleotide sequences encoding portions (fragments), or encoding variant polypeptides such as analogues or derivatives of an
10 *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide. Such variants can be naturally-occurring, such as in the case of allelic variation or single nucleotide polymorphisms, or non-naturally-occurring, such as those induced by various mutagens and mutagenic processes. Intended variations include, but are not limited to, addition, deletion, and substitution of one or more
15 nucleotides that can result in conservative or non-conservative amino acid changes, including additions and deletions. Preferably, the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleotide (and/or resultant amino acid) changes are silent or conserved; that is, they do not alter the characteristics or activity of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*,
20 *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide. In one preferred embodiment, the nucleotide sequences are fragments that comprise one or more polymorphic microsatellite markers.

Other alterations of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecules of the invention can
25 include, for example, labeling, methylation, internucleotide modifications such as uncharged linkages (*e.g.*, methyl phosphonates, phosphotriesters, phosphoamidates, and carbamates), charged linkages (*e.g.*, phosphorothioates or phosphorodithioates), pendent moieties (*e.g.*, polypeptides), intercalators (*e.g.*, acridine or psoralen), chelators, alkylators, and modified linkages (*e.g.*, alpha anomeric nucleic acids).
30 Also included are synthetic molecules that mimic nucleic acid molecules in the ability to bind to a designated sequences via hydrogen bonding and other chemical

interactions. Such molecules include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule.

The invention also pertains to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid molecules that hybridize under high stringency hybridization conditions, such as for selective hybridization, to a nucleotide sequence described herein (e.g., nucleic acid molecules that specifically hybridize to a nucleotide sequence encoding polypeptides described herein, and, optionally, have an activity of the polypeptide). In one embodiment, the invention includes variants described herein that hybridize under high stringency hybridization conditions (e.g., for selective hybridization) to a nucleotide sequence comprising a nucleotide sequence selected from SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9 and the complement of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9. In another embodiment, the invention includes variants described herein that hybridize under high stringency hybridization conditions (e.g., for selective hybridization) to a nucleotide sequence encoding an amino acid sequence of SEQ ID NO: 2 (*HDAC9*), SEQ ID NO: 4 (*HDAC9a*), SEQ ID NO: 6 (*HDAC9(ΔNLS)*), SEQ ID NO: 8 (*HDAC9a(ΔNLS)*), or SEQ ID NO: 10 (*HDRP(ΔNLS)*). In a preferred embodiment, the variant that hybridizes under high stringency hybridizations encodes a polypeptide that has a biological activity of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide (e.g., histone deacetylase activity or transcription repression activity).

Such nucleic acid molecules can be detected and/or isolated by specific hybridization (e.g., under high stringency conditions). "Specific hybridization," as used herein, refers to the ability of a first nucleic acid to hybridize to a second nucleic acid in a manner such that the first nucleic acid does not hybridize to any nucleic acid other than to the second nucleic acid (e.g., when the first nucleic acid has a higher similarity to the second nucleic acid than to any other nucleic acid in a sample wherein the hybridization is to be performed). "Stringency conditions" for hybridization is a term of art that refers to the incubation and wash conditions, e.g., conditions of temperature and buffer concentration, that permit hybridization of a particular nucleic acid to a second nucleic acid; the first nucleic acid may be

- perfectly (*i.e.*, 100%) complementary to the second, or the first and second may share some degree of complementarity that is less than perfect (*e.g.*, 70%, 75%, 85%, 95%). For example, certain high stringency conditions can be used that distinguish perfectly complementary nucleic acids from those of less
- 5 complementarity. "High stringency conditions," "moderate stringency conditions," and "low stringency conditions" for nucleic acid hybridizations are explained on pages 2.10.1-2.10.16 and pages 6.3.1-6.3.6 in *Current Protocols in Molecular Biology* (See Ausubel *et al.*, *supra*, the entire teachings of which are incorporated by reference herein). The exact conditions that determine the stringency of
- 10 hybridization depend not only on ionic strength (*e.g.*, 0.2XSSC or 0.1XSSC), temperature (*e.g.*, room temperature, 42°C or 68°C), and the concentration of destabilizing agents such as formamide or denaturing agents such as SDS, but also on factors such as the length of the nucleic acid sequence, base composition, percent mismatch between hybridizing sequences, and the frequency of occurrence of
- 15 subsets of that sequence within other non-identical sequences. Thus, equivalent conditions can be determined by varying one or more of these parameters while maintaining a similar degree of identity or similarity between the two nucleic acid molecules. Typically, conditions are used such that sequences at least about 60%, at least about 70%, at least about 80%, at least about 90% or at least about 95% or
- 20 more identical to each other remain hybridized to one another. By varying hybridization conditions from a level of stringency at which no hybridization occurs to a level at which hybridization is first observed, conditions that will allow a given sequence to hybridize (*e.g.*, selectively) with the most similar sequences in the sample can be determined.
- 25 Exemplary conditions are described in Krause and Aaronson, *Methods in Enzymology*, 200:546-556 (1991). Also, in, Ausubel, *et al.*, *supra*, which describes the determination of washing conditions for moderate or low stringency conditions. Washing is the step in which conditions are usually set so as to determine a minimum level of complementarity of the hybrids. Generally, starting from the
- 30 lowest temperature at which only homologous hybridization occurs, each °C by which the final wash temperature is reduced (holding SSC concentration constant) allows an increase by 1% in the maximum extent of mismatching among the

sequences that hybridize. Generally, doubling the concentration of SSC results in an increase in T_m of 17°C. Using these guidelines, the washing temperature can be determined empirically for high, moderate, or low stringency, depending on the level of mismatch sought.

5 For example, a low stringency wash can comprise washing in a solution containing 0.2XSSC/0.1% SDS for 10 minutes at room temperature; a moderate stringency wash can comprise washing in a prewarmed solution (42°C) solution containing 0.2XSSC/0.1% SDS for 15 minutes at 42°C; and a high stringency wash can comprise washing in prewarmed (68°C) solution containing 0.1XSSC/0.1%SDS
10 for 15 minutes at 68°C. Furthermore, washes can be performed repeatedly or sequentially to obtain a desired result as known in the art. Equivalent conditions can be determined by varying one or more of the parameters given as an example, as known in the art, while maintaining a similar degree of identity or similarity between the target nucleic acid molecule and the primer or probe used.

15 To determine the percent homology or identity of two nucleic acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of one polypeptide or nucleic acid molecule for optimal alignment with the other polypeptide or nucleic acid molecule). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide
20 positions are then compared, as described above.

 The present invention also provides isolated *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid molecules that contain a fragment or portion that hybridizes under highly stringent conditions to a nucleotide sequence comprising a nucleotide sequence selected from SEQ ID NO: 1,
25 SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and the complement of any of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9 and also provides isolated nucleic acid molecules that contain a fragment or portion that hybridizes under highly stringent conditions to a nucleotide sequence encoding an amino acid sequence selected from SEQ ID NO: 2, SEQ ID NO: 4, SEQ
30 ID NO: 6, SEQ ID NO: 8, and SEQ ID NO: 10. The nucleic acid fragments of the invention are at least about 15, preferably, at least about 18, 20, 23, or 25 nucleotides, and can be 30, 40, 50, 100, 200 or more nucleotides in length. Longer

fragments, for example, 30 or more nucleotides in length, that encode antigenic polypeptides described herein are particularly useful, such as for the generation of antibodies as described above.

In a related aspect, the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*,
5 and *HDRP(ΔNLS)* nucleic acid fragments of the invention are used as probes or primers in assays such as those described herein. "Probes" or "primers" are oligonucleotides that hybridize in a base-specific manner to a complementary strand of nucleic acid molecules. Such probes and primers include polypeptide nucleic acids, as described in Nielsen *et al.*, Science, 254, 1497-1500 (1991). As also used
10 herein, the term "primer" in particular refers to a single-stranded oligonucleotide that acts as a point of initiation of template-directed DNA synthesis using well-known methods (*e.g.*, PCR, LCR) including, but not limited to those described herein.

Typically, a probe or primer comprises a region of nucleotide sequence that hybridizes to at least about 15, typically about 20-25, and more typically about 40,
15 50 or 75, consecutive nucleotides of a nucleic acid molecule comprising a contiguous nucleotide sequence selected from: SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, the complement of any of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and a sequence encoding an amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6,
20 SEQ ID NO: 8, or SEQ ID NO: 10.

In preferred embodiments, a probe or primer comprises 100 or fewer nucleotides, preferably, from 6 to 50 nucleotides, and more preferably, from 12 to 30 nucleotides. In other embodiments, the probe or primer is at least 70% identical to the contiguous nucleotide sequence or to the complement of the contiguous
25 nucleotide sequence, preferably, at least 80% identical, more preferably, at least 90% identical, even more preferably, at least 95% identical, or even capable of selectively hybridizing to the contiguous nucleotide sequence or to the complement of the contiguous nucleotide sequence. Often, the probe or primer further comprises a label, *e.g.*, radioisotope, fluorescent compound, enzyme, or enzyme co-factor.

30 The nucleic acid molecules of the invention such as those described above can be identified and isolated using standard molecular biology techniques and the sequence information provided in SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5,

SEQ ID NO: 7, SEQ ID NO: 9, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, and /or SEQ ID NO: 10. For example, nucleic acid molecules can be amplified and isolated by the polymerase chain reaction using synthetic oligonucleotide primers designed based on one or more of the nucleic acid sequences provided above and/or the complement of those sequences. Or such nucleic acid molecules may be designed based on nucleotide sequences encoding one or more of the amino acid sequences provided in SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. See generally PCR Technology: Principles and Applications for DNA Amplification (ed. H.A. Erlich, Freeman Press, NY, NY, (1992); PCR Protocols: A Guide to Methods and Applications (Eds. Innis *et al.*, Academic Press, San Diego, CA, (1990); Mattila *et al.*, Nucleic Acids Res., 19: 4967 (1991); Eckert *et al.*, PCR Methods and Applications, 1: 17 (1991); PCR (eds. McPherson *et al.*, IRL Press, Oxford)); and U.S. Patent No. 4,683,202. The nucleic acid molecules can be amplified using cDNA, mRNA, or genomic DNA as a template, cloned into an appropriate vector and characterized by DNA sequence analysis.

Other suitable amplification methods include the ligase chain reaction (LCR) (See Wu and Wallace, Genomics, 4:560 (1989), Landegren *et al.*, Science, 241:1077 (1988)), transcription amplification (Kwoh *et al.*, Proc. Natl. Acad. Sci. USA, 86:1173 (1989)), and self-sustained sequence replication (See Guatelli *et al.*, Proc. Nat. Acad. Sci. USA, 87:1874 (1990)) and nucleic acid based sequence amplification (NASBA). The latter two amplification methods involve isothermal reactions based on isothermal transcription, that produce both single stranded RNA (ssRNA) and double stranded DNA (dsDNA) as the amplification products in a ratio of about 30 or 100 to 1, respectively.

The amplified DNA can be radiolabeled and used as a probe for screening a cDNA library derived from human cells, mRNA in zap express, ZIPLOX, or other suitable vector. Corresponding clones can be isolated, DNA can be obtained following *in vivo* excision, and the cloned insert can be sequenced in either or both orientations by art-recognized methods to identify the correct reading frame encoding a polypeptide of the appropriate molecular weight. For example, the direct analysis of the nucleotide sequence of nucleic acid molecules of the present

invention can be accomplished using well-known methods that are commercially available. See, for example, Sambrook *et al.*, Molecular Cloning, A Laboratory Manual (2nd Ed., CSHP, New York (1989)); Zyskind *et al.*, Recombinant DNA Laboratory Manual, (Acad. Press, (1988)). Using these or similar methods, the
5 polypeptide and the DNA encoding the polypeptide can be isolated, sequenced, and further characterized.

Antisense nucleic acid molecules of the invention can be designed using the nucleotide sequences of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9 and/or the complement of any of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9 and/or a portion of those
10 sequences, and/or the complement of those portion or sequences, and/or a sequence encoding the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or encoding a portion of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. Such antisense nucleic
15 acid molecules can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid molecule (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability
20 of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Alternatively, the antisense nucleic acid molecule can be produced biologically using an expression vector into which a nucleic acid molecule has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid molecule
25 will be of an antisense orientation to a target nucleic acid of interest).

In general, the isolated *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid sequences of the invention can be used as molecular weight markers on Southern blots, and as chromosome markers that are labeled to map related gene positions. The nucleic acid sequences can also be used to compare
30 with endogenous DNA sequences in patients to identify genetic disorders (*e.g.*, a predisposition for or susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease), and as probes, such as to hybridize and

discover related DNA sequences or to subtract out known sequences from a sample. The nucleic acid molecules of the present invention can also be used as therapeutic agents.

By a "cell proliferation disease" is meant a disease that is caused by or results in undesirably high levels of cell division, undesirably low levels of apoptosis, or both. For example, cancers such as lymphoma, leukemia, melanoma, ovarian cancer, breast cancer, pancreatic cancer, prostate cancer, colon cancer, and lung cancer are all examples of cell proliferation diseases. Myeloproliferative disorders, including polycythemia vera, essential thrombocythemia, agnogenic myeloid metaplasia, and chronic myelogenous leukemia are also cell proliferation diseases.

By a "cell differentiation disease" is meant a disease that is caused by or results in undesirably low levels of cell differentiation, or by undesirably high levels of cell differentiation. For example, cancers such as lymphoma, leukemia, melanoma, ovarian cancer, breast cancer, pancreatic cancer, prostate cancer, colon cancer, and lung cancer are all examples of cell differentiation diseases. Myeloproliferative disorders, including polycythemia vera, essential thrombocythemia, agnogenic myeloid metaplasia, and chronic myelogenous leukemia are also cell differentiation diseases.

By an "apoptotic disease" is meant a condition in which the apoptotic response is abnormal. This may pertain to a cell or a population of cells that does not undergo cell death under appropriate conditions. For example, normally a cell will die upon exposure to apoptotic-triggering agents, such as chemotherapeutic agents, or ionizing radiation. When, however, a subject has an apoptotic disease, for example, cancer, the cell or a population of cells may not undergo cell death in response to contact with apoptotic-triggering agents. In addition, a subject may have an apoptotic disease when the occurrence of cell death is too low, for example, when the number of proliferating cells exceeds the number of cells undergoing cell death, as occurs in cancer when such cells do not properly differentiate.

An apoptotic disease may also be a condition characterized by the occurrence of undesirably high levels of apoptosis. For example, certain neurodegenerative diseases, including but not limited to Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, restenosis, stroke, and ischemic

brain injury are apoptotic diseases in which neuronal cells undergo undesired cell death.

Other diseases for which the polypeptides and nucleic acid molecules of the present invention may be useful for diagnosing and/or treating include, but are not
5 limited to Huntington's disease.

The *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleic acid molecules of the present invention can further be used to derive primers for genetic fingerprinting, to raise anti-polypeptide antibodies using DNA immunization techniques, and as an antigen to raise anti-DNA antibodies or
10 elicit immune responses. Portions or fragments of the nucleotide sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. For example, these sequences can be used to: (i) map their respective genes on a chromosome; and, thus, locate gene regions associated with genetic disease; (ii) identify an individual from a minute
15 biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample.

In addition, the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, and *HDRP(ΔNLS)* nucleotide sequences of the invention can be used to identify and express recombinant polypeptides for analysis, characterization, or therapeutic use,
20 or as markers for tissues in which the corresponding polypeptide is expressed, either constitutively, during tissue differentiation, or in diseased states. The nucleic acid sequences can additionally be used as reagents in the screening and/or diagnostic assays described herein, and can also be included as components of kits (e.g., reagent kits) for use in the screening and/or diagnostic assays described herein.

Standard techniques, such as the polymerase chain reaction (PCR) and DNA hybridization, may be used to clone *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*,
25 *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* homologs in other species, for example, mammalian homologs. *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* homologs may be readily identified using low-stringency DNA
30 hybridization or low-stringency PCR with human *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* probes or primers. Degenerate primers encoding human *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or

HDRP(Δ NLS) polypeptides may be used to clone *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* homologs by RT-PCR.

Alternatively, additional *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* homologs can be identified by utilizing
5 consensus sequence information for *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* polypeptides to search for similar polypeptides in other species. For example, polypeptide databases for other species can be searched for proteins with the HDAC domains described herein. Candidate polypeptides containing such a motif can then be tested for their *HDAC9*, *HDAC9a*,
10 *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* biological activities, using methods described herein.

EXPRESSION OF THE NUCLEIC ACID MOLECULES OF THE INVENTION

Another aspect of the invention pertains to nucleic acid constructs containing
15 an *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule, for example, one selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, and the complement of any of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9 (or portions thereof). Yet another aspect of the invention
20 pertains to *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, and *HDRP(Δ NLS)* nucleic acid constructs containing a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. The constructs comprise a vector (*e.g.*, an expression vector) into which a sequence of the invention has been inserted in a sense or antisense orientation.

25 As used herein, the term "vector" or "construct" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid," which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral
30 genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal

mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors, expression vectors, are capable of directing the expression of genes to which they are operably linked. In general, expression vectors of utility in

- 5 recombinant DNA techniques are often in the form of plasmids. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses) that serve equivalent functions.

- Preferred recombinant expression vectors of the invention comprise a nucleic
10 acid molecule of the invention in a form suitable for expression of the nucleic acid molecule in a host cell. This means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to
15 mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner that allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals).
20 Such regulatory sequences are described, for example, in Goeddel, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). Regulatory sequences include those that direct constitutive expression of a nucleotide sequence in many types of host cell and those that direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory
25 sequences).

- It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed and the level of expression of polypeptide desired. The expression vectors of the invention can be introduced into host cells to thereby produce
30 polypeptides, including fusion polypeptides, encoded by nucleic acid molecules as described herein.

The recombinant expression vectors of the invention can be designed for expression of a polypeptide of the invention in prokaryotic or eukaryotic cells, *e.g.*, bacterial cells, such as *E. coli*, insect cells (using baculovirus expression vectors), yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, 5 *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example, using T7 promoter regulatory sequences and T7 polymerase.

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms 10 "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included 15 within the scope of the term as used herein.

A host cell can be any prokaryotic or eukaryotic cell. For example, a nucleic acid molecule of the invention can be expressed in bacterial cells (*e.g.*, *E. coli*), insect cells, yeast, or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells, human 293T cells, HeLa cells, NIH 3T3 cells, and mouse 20 erythroleukemia (MEL) cells). Other suitable host cells are known to those skilled in the art.

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of 25 art-recognized techniques for introducing a foreign nucleic acid molecule (*e.g.*, DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (*supra*), and other laboratory manuals.

30 For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select

these integrants, a gene that encodes a selectable marker (*e.g.*, for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those that confer resistance to drugs, such as G418, hygromycin, or methotrexate. Nucleic acid molecules encoding a selectable
5 marker can be introduced into a host cell on the same vector as the nucleic acid molecule of the invention or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid molecule can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker gene will survive, while the other cells die).

10 A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (*i.e.*, express) a polypeptide of the invention. Accordingly, the invention further provides methods for producing a polypeptide using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector
15 encoding a polypeptide of the invention has been introduced) in a suitable medium such that the polypeptide is produced. In another embodiment, the method further comprises isolating the polypeptide from the medium or the host cell.

The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is
20 a fertilized oocyte or an embryonic stem cell into which an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule of the invention has been introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous nucleotide sequences have been introduced into the genome or homologous recombinant animals in which
25 endogenous nucleotide sequences have been altered. Such animals are useful for studying the function and/or activity of the nucleotide sequence and polypeptide encoded by the sequence and for identifying and/or evaluating modulators of their activity.

As used herein, a “transgenic animal” is a non-human animal, preferably, a
30 mammal, more preferably, a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, and amphibians. A

transgene is exogenous DNA that is integrated into the genome of a cell from which a transgenic animal develops and that remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, a "homologous
5 recombinant animal" is a non-human animal, preferably, a mammal, more preferably, a mouse, in which an endogenous gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

10 Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Patent No. 4,873,191, and in Hogan, *Manipulating the Mouse Embryo* (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., (1986)). Methods for
15 constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley, *Current Opinion in Bio/Technology*, 2:823-829 (1991) and in PCT Publication Nos. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169. Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut *et al.*,
20 *Nature*, 385:810-813 (1997) and PCT Publication Nos. WO 97/07668 and WO 97/07669.

ANTIBODIES OF THE INVENTION

Polyclonal and/or monoclonal antibodies that selectively bind one form of an
25 HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide but not another form of the polypeptide are also provided. Antibodies are also provided that bind a portion of either the variant or reference HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide that contains the polymorphic site or sites.

30 In another aspect, the invention provides antibodies to each of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS) polypeptides and polypeptide fragments of the invention, *e.g.*, having an amino acid sequence encoded

by SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10,
or a portion thereof, or having an amino acid sequence encoded by a nucleic acid
molecule comprising all or a portion of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO:
5, SEQ ID NO: 7, or SEQ ID NO: 9, (*e.g.*, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID
5 NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10, or another variant, or portion thereof).

The term "purified antibody" as used herein refers to immunoglobulin
molecules and immunologically active portions of immunoglobulin molecules, *i.e.*,
molecules that contain an antigen binding site that selectively binds an antigen. A
molecule that selectively binds to a polypeptide of the invention is a molecule that
10 binds to that polypeptide or a fragment thereof, but does not substantially bind other
molecules in a sample, *e.g.*, a biological sample that naturally contains the
polypeptide. Preferably the antibody is at least 60%, by weight, free from proteins
and naturally occurring organic molecules with which it naturally associated. More
preferably, the antibody preparation is at least 75% or 90%, and most preferably,
15 99%, by weight, antibody. Examples of immunologically active portions of
immunoglobulin molecules include F(ab) and F(ab')₂ fragments that can be
generated by treating the antibody with an enzyme such as pepsin.

The invention provides polyclonal and monoclonal antibodies that selectively
bind to an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS)
20 polypeptide of the invention. The term "monoclonal antibody" or "monoclonal
antibody composition," as used herein, refers to a population of antibody molecules
that contain only one species of an antigen binding site capable of immunoreacting
with a particular epitope of a polypeptide of the invention. A monoclonal antibody
composition thus typically displays a single binding affinity for a particular
25 polypeptide of the invention with which it immunoreacts.

Polyclonal antibodies can be prepared as described above by immunizing a
suitable subject with a desired immunogen, *e.g.*, an HDAC9, HDAC9a,
HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide of the invention or
fragment thereof. The antibody titer in the immunized subject can be monitored
30 over time by standard techniques, such as with an enzyme linked immunosorbent
assay (ELISA) using immobilized polypeptide. If desired, the antibody molecules
directed against the polypeptide can be isolated from the mammal (*e.g.*, from the

blood) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction.

At an appropriate time after immunization, *e.g.*, when the antibody titers are highest, antibody-producing cells can be obtained from the subject and used to

5 prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein, *Nature*, 256:495-497 (1975), the human B cell hybridoma technique (Kozbor *et al.*, *Immunol. Today*, 4:72 (1983)), the EBV-hybridoma technique (Cole *et al.*, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96 (1985)) or trioma techniques. The

10 technology for producing hybridomas is well known (see generally *Current Protocols in Immunology*, Coligan *et al.*, (eds.) John Wiley & Sons, Inc., New York, NY (1994)). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with an immunogen as described above, and the culture supernatants of the resulting hybridoma cells are screened to

15 identify a hybridoma producing a monoclonal antibody that binds a polypeptide of the invention.

Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating a monoclonal antibody to a polypeptide of the invention (see, *e.g.*, *Current Protocols in*

20 *Immunology, supra*; Galfre *et al.*, (1977) *Nature*, 266:55052; R.H. Kenneth, in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York, New York (1980); and Lerner, *Yale J. Biol. Med.*, 54:387-402 (1981)). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods that also would be useful.

25 Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody to an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with the polypeptide to thereby isolate immunoglobulin

30 library members that bind the polypeptide. Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia Recombinant Phage Antibody System, Catalog No. 27-9400-01; and the Stratagene SurfZAP™ Phage

Display Kit, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; 5 PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs *et al.*, *Bio/Technology*, 9:1370-1372 (1991); Hay *et al.*, *Hum. Antibod. Hybridomas*, 3:81-85 (1992); Huse *et al.*, *Science*, 246:1275-1281 (1989); and Griffiths *et al.*, *EMBO J.*, 12:725-734 (1993).

10 Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art.

15 In general, antibodies of the invention (*e.g.*, a monoclonal antibody) can be used to isolate an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide of the invention by standard techniques, such as affinity chromatography or immunoprecipitation. A polypeptide-specific antibody can facilitate the purification of natural polypeptide from cells and of recombinantly 20 produced polypeptide expressed in host cells. Moreover, an antibody specific for an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide of the invention can be used to detect the polypeptide (*e.g.*, in a cellular lysate, cell supernatant, or tissue sample) in order to evaluate the abundance and pattern of expression of the polypeptide.

25 The antibodies of the present invention can also be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent 30 materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β -galactosidase, and acetylcholinesterase; examples of suitable

prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride and phycoerythrin; an example of a luminescent material includes luminol; examples of
5 bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S , and ^3H .

DIAGNOSTIC AND SCREENING ASSAYS OF THE INVENTION

The present invention also pertains to diagnostic assays for assessing *HDAC*
10 *9 HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* gene expression, or for assessing activity of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptides of the invention. In one embodiment, the assays are used in the context of a biological sample (*e.g.*, blood, serum, cells, tissue) to thereby determine whether an individual is afflicted with a cell proliferation disease,
15 an apoptotic disease, or a cell differentiation disease, or is at risk for (has a predisposition for or a susceptibility to) developing a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. The invention also provides for prognostic (or predictive) assays for determining whether an individual is susceptible to developing a cell proliferation disease, an apoptotic disease, or a cell
20 differentiation disease. For example, mutations in the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule can be assayed in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of symptoms associated with a cell proliferation disease, an apoptotic disease, or a cell
25 differentiation disease.

Another aspect of the invention pertains to assays for monitoring the influence of agents, or candidate compounds (*e.g.*, drugs or other agents) on the nucleic acid molecule expression or biological activity of polypeptides of the invention, as well as to assays for identifying candidate compounds that bind to an
30 *HDAC9*, *HDAC9a* polypeptide, an *HDAC9(ΔNLS)* polypeptide, an *HDAC9a(ΔNLS)* polypeptide, or an *HDRP(ΔNLS)* polypeptide. These and other assays and agents are described in further detail in the following sections.

DIAGNOSTIC ASSAYS

HDAC9, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecules, probes, primers, polypeptides, and antibodies to an *HDAC9*,
5 an *HDAC9a* protein, an *HDAC9(ΔNLS)* protein, an *HDAC9a(ΔNLS)* protein, or an *HDRP(ΔNLS)* protein can be used in methods of diagnosis of a susceptibility to, or likelihood of having a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, as well as in kits useful for diagnosis of a susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

10 In one embodiment of the invention, diagnosis of a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease is made by detecting a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. The polymorphism can be a mutation in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, such as the
15 insertion or deletion of a single nucleotide, or of more than one nucleotide, resulting in a frame shift mutation; the change of at least one nucleotide, resulting in a change in the encoded amino acid; the change of at least one nucleotide, resulting in the generation of a premature stop codon; the deletion of several nucleotides, resulting in a deletion of one or more amino acids encoded by the nucleotides; the insertion of
20 one or several nucleotides, such as by unequal recombination or gene conversion, resulting in an interruption of the coding sequence of the gene; duplication of all or a part of the gene; transposition of all or a part of the gene; or rearrangement of all or a part of the gene, or a change in the expression pattern of the various *HDAC9* isoforms. More than one such mutation may be present in a single nucleic acid
25 molecule.

Such sequence changes cause a mutation in the polypeptide encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. For example, if the mutation is a frame shift mutation, the frame shift can result in a change in the encoded amino acids, and/or can result in the generation of a
30 premature stop codon, causing generation of a truncated polypeptide. Alternatively, a polymorphism associated with a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease can be a synonymous

mutation in one or more nucleotides (*i.e.*, a mutation that does not result in a change in the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide). Such a polymorphism may alter sites, affect the stability or transport of mRNA, or otherwise affect the transcription or translation of the nucleic acid molecule. HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) that has any of the mutations described above is referred to herein as a "mutant nucleic acid molecule."

In a first method of diagnosing a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, hybridization methods, such as Southern analysis, Northern analysis, or *in situ* hybridizations, can be used (see Ausubel, *et al.*, *supra*). For example, a biological sample from a test subject (a "test sample") of genomic DNA, RNA, or cDNA, is obtained from an individual suspected of having, being susceptible to or predisposed for, or carrying a defect for, a cell proliferation disease, an apoptotic disease, or a cell differentiation disease (the "test individual"). The individual can be an adult, child, or fetus. The test sample can be from any source that contains genomic DNA, such as a blood sample, sample of amniotic fluid, sample of cerebrospinal fluid, or tissue sample from skin, muscle, buccal or conjunctival mucosa, placenta, gastrointestinal tract, or other organs. A test sample of DNA from fetal cells or tissue can be obtained by appropriate methods, such as by amniocentesis or chorionic villus sampling. The DNA, RNA, or cDNA sample is then examined to determine whether a polymorphism in HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) is present, and/or to determine which variant(s) encoded by HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) is present. The presence of the polymorphism or variant(s) can be indicated by hybridization of the gene in the genomic DNA, RNA, or cDNA to a nucleic acid probe. A "nucleic acid probe," as used herein, can be a DNA probe or an RNA probe; the nucleic acid probe can contain at least one polymorphism in HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) or contains a nucleic acid encoding a particular variant of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS). The probe can be any of the nucleic acid

molecules described above (e.g., the entire nucleic acid molecule, a fragment, a vector comprising the gene, a probe, or primer, etc.).

To diagnose a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, a hybridization sample is formed
5 by contacting the test sample containing *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, with at least one nucleic acid probe. A preferred probe for detecting mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* mRNA or genomic DNA sequences described herein. The nucleic
10 acid probe can be, for example, a full-length nucleic acid molecule, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250, or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to appropriate mRNA or genomic DNA. For example, the nucleic acid probe can be all or a portion of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ
15 ID NO: 7, SEQ ID NO: 9, or the complement of SEQ ID NO: 1 or SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9; or can be a nucleic acid molecule encoding all or a portion of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10. Other suitable probes for use in the diagnostic assays of the invention are described above (see. e.g., probes and primers discussed under the
20 heading, "Nucleic Acids of the Invention").

The hybridization sample is maintained under conditions that are sufficient to allow specific hybridization of the nucleic acid probe to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. "Specific hybridization," as used herein, indicates exact hybridization (e.g., with no mismatches). Specific
25 hybridization can be performed under high stringency conditions or moderate stringency conditions, for example, as described above. In a particularly preferred embodiment, the hybridization conditions for specific hybridization are high stringency.

Specific hybridization, if present, is then detected using standard methods. If
30 specific hybridization occurs between the nucleic acid probe and *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* in the test sample, then *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* has the

polymorphism, or is the variant, that is present in the nucleic acid probe. More than one nucleic acid probe can also be used concurrently in this method. Specific hybridization of any one of the nucleic acid probes is indicative of a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or of the presence of a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and is therefore diagnostic for a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

In Northern analysis (see Current Protocols in Molecular Biology, Ausubel, *et al.*, *supra*), the hybridization methods described above are used to identify the presence of a polymorphism or of a particular variant, associated with a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. For Northern analysis, a test sample of RNA is obtained from the individual by appropriate means. Specific hybridization of a nucleic acid probe, as described above, to RNA from the individual is indicative of a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or of the presence of a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and is therefore diagnostic for a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

For representative examples of use of nucleic acid probes, see, for example, U.S. Patent Nos. 5,288,611 and 4,851,330.

Alternatively, a peptide nucleic acid (PNA) probe can be used instead of a nucleic acid probe in the hybridization methods described above. PNA is a DNA mimic having a peptide-like, inorganic backbone, such as N-(2-aminoethyl)glycine units, with an organic base (A, G, C, T, or U) attached to the glycine nitrogen via a methylene carbonyl linker (see, for example, Nielsen *et al.*, *Bioconjugate Chemistry*, 5 (1994), American Chemical Society, p. 1 (1994)). The PNA probe can be designed to specifically hybridize to a gene having a polymorphism associated with a susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. Hybridization of the PNA probe to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* is diagnostic for a decreased

susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

In another method of the invention, mutation analysis by restriction digestion can be used to detect a mutant nucleic acid molecule, or nucleic acid molecules containing a polymorphism(s), if the mutation or polymorphism in the gene results in the creation or elimination of a restriction site. A test sample containing genomic DNA is obtained from the individual. Polymerase chain reaction (PCR) can be used to amplify *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (and, if necessary, the flanking sequences) in the test sample of genomic DNA from the test individual. RFLP analysis is conducted as described (see Current Protocols in Molecular Biology, *supra*). The digestion pattern of the relevant DNA fragment indicates the presence or absence of the mutation or polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and therefore indicates the presence or absence of this decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

Sequence analysis can also be used to detect specific polymorphisms in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. A test sample of DNA or RNA is obtained from the test individual. PCR or other appropriate methods can be used to amplify the nucleic acid molecule, and/or its flanking sequences, if desired. The sequence of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or a fragment of the any of those nucleic acid molecules, or an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* cDNA, or a fragment of any of those cDNAs, or an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* mRNA, or a fragment of any of those mRNAs, is determined, using standard methods. The sequence of the above gene, gene fragment, cDNA, cDNA fragment, mRNA, or mRNA fragment is compared with the known nucleic acid sequence of the nucleic acid molecule, cDNA (e.g., SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or a nucleic acid sequence encoding the protein of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or a fragment thereof) or mRNA, as appropriate. The presence of a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* indicates that the

individual has a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

Allele-specific oligonucleotides can also be used to detect the presence of a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or
5 *HDRP(ΔNLS)*, through the use of dot-blot hybridization of amplified oligonucleotides with allele-specific oligonucleotide (ASO) probes (see, for example, Saiki *et al.*, Nature (London) 324:163-166 (1986)). An "allele-specific oligonucleotide" (also referred to herein as an "allele-specific oligonucleotide probe") is an oligonucleotide of approximately 10-50 base pairs, preferably
10 approximately 15-30 base pairs, that specifically hybridizes to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and that contains a polymorphism associated with a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. An allele-specific oligonucleotide probe that is specific for particular polymorphisms in *HDAC9*,
15 *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* can be prepared, using standard methods (see Current Protocols in Molecular Biology, *supra*).

To identify polymorphisms in the gene that are associated with a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease a test sample of DNA is obtained from the individual. PCR
20 can be used to amplify all or a fragment of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and its flanking sequences. The DNA containing the amplified *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (or a fragment of any of those genes) is dot-blotted, using standard methods (see Current Protocols in Molecular Biology, *supra*), and the blot is
25 contacted with the oligonucleotide probe. The presence of specific hybridization of the probe to the amplified *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* is then detected. Specific hybridization of an allele-specific oligonucleotide probe to DNA from the individual is indicative of a polymorphism in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, and is
30 therefore indicative of a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

In another embodiment, arrays of oligonucleotide probes that are complementary to target nucleic acid sequence segments from an individual, can be used to identify polymorphisms in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. For example, in one embodiment, an

5 oligonucleotide array can be used. Oligonucleotide arrays typically comprise a plurality of different oligonucleotide probes that are coupled to a surface of a substrate in different known locations. These oligonucleotide arrays, also described as "GENECHIPS™," have been generally described in the art, for example, U.S. Patent No. 5,143,854 and PCT patent publication Nos. WO 90/15070 and 92/10092.

10 These arrays can generally be produced using mechanical synthesis methods or light directed synthesis methods that incorporate a combination of photolithographic methods and solid phase oligonucleotide synthesis methods. See Fodor *et al.*, Science, 251:767-777 (1991), Pirrung *et al.*, U.S. Patent No. 5,143,854; PCT Publication No. WO 90/15070; Fodor *et al.*, PCT Publication No. WO 92/10092,

15 and U.S. Patent No. 5,424,186, the entire teachings of each of which are incorporated by reference herein. Techniques for the synthesis of these arrays using mechanical synthesis methods are described in, *e.g.*, U.S. Patent No. 5,384,261, the entire teachings of which are incorporated by reference herein.

Once an oligonucleotide array is prepared, a nucleic acid of interest is

20 hybridized to the array and scanned for polymorphisms. Hybridization and scanning are generally carried out by methods described herein and also in, *e.g.*, Published PCT Application Nos. WO 92/10092 and WO 95/11995, and U.S. Patent No. 5,424,186, the entire teachings of which are incorporated by reference herein. In brief, a target nucleic acid sequence that includes one or more previously identified

25 polymorphic markers is amplified by well known amplification techniques, *e.g.*, PCR. Typically, this involves the use of primer sequences that are complementary to the two strands of the target sequence both upstream and downstream from the polymorphism. Asymmetric PCR techniques may also be used. Amplified target, generally incorporating a label, is then hybridized with the array under appropriate

30 conditions. Upon completion of hybridization and washing of the array, the array is scanned to determine the position on the array to which the target sequence

hybridizes. The hybridization data obtained from the scan is typically in the form of fluorescence intensities as a function of location on the array.

Although primarily described in terms of a single detection block, *e.g.*, for detection of a single polymorphism, arrays can include multiple detection blocks, and thus be capable of analyzing multiple, specific polymorphisms. In alternate arrangements, it will generally be understood that detection blocks may be grouped within a single array or in multiple, separate arrays so that varying, optimal conditions may be used during the hybridization of the target to the array. For example, it may often be desirable to provide for the detection of those polymorphisms that fall within G-C rich stretches of a genomic sequence, separately from those falling in A-T rich segments. This allows for the separate optimization of hybridization conditions for each situation.

Additional descriptions of the use of oligonucleotide arrays for detection of polymorphisms can be found, for example, in U.S. Patent Nos. 5,858,659 and 5,837,832, the entire teachings of which are incorporated by reference herein.

Other methods of nucleic acid analysis can be used to detect polymorphisms in *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* or variants encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. Representative methods include direct manual sequencing (Church and Gilbert Proc. Natl. Acad. Sci. USA 81: 1991-1995, (1988); Sanger *et al.*, Proc. Natl. Acad. Sci. 74: 5463-5467 (1977); Beavis *et al.*, U.S. Patent No. 5,288,644); automated fluorescent sequencing; single-stranded conformation polymorphism assays (SSCP); clamped denaturing gel electrophoresis (CDGE); denaturing gradient gel electrophoresis (DGGE) (Sheffield *et al.*, Proc. Natl. Acad. Sci. USA 86: 232-236 (1991)), mobility shift analysis (Orita *et al.*, Proc. Natl. Acad. Sci. USA 86: 2766-2770 (1989)), restriction enzyme analysis (Flavell *et al.*, Cell 15: 25 (1978); Geever, *et al.*, Proc. Natl. Acad. Sci. USA 78: 5081 (1981)); heteroduplex analysis; chemical mismatch cleavage (CMC) (Cotton *et al.*, Proc. Natl. Acad. Sci. USA 85: 4397-4401 (1985)); RNase protection assays (Myers *et al.*, Science 230: 1242 (1985)); use of polypeptides that recognize nucleotide mismatches, such as *E. coli* mutS protein; and allele-specific PCR.

In another embodiment of the invention, diagnosis of a susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease can also be made by examining the level of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid, for example, using in situ hybridization techniques known to one skilled in the art, or by examining the level of expression, activity, and/or composition of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide, by a variety of methods, including enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, immunohistochemistry, and immunofluorescence. A test sample from an individual is assessed for the presence of an alteration in the level of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid or in the expression and/or an alteration in composition of the polypeptide encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or for the presence of a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. An alteration in expression of a polypeptide encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* can be, for example, an alteration in the quantitative polypeptide expression (*i.e.*, the amount of polypeptide produced); an alteration in the composition of a polypeptide encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or an alteration in the qualitative polypeptide expression (*e.g.*, expression of a mutant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide or variant thereof). In a preferred embodiment, diagnosis of a susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease is made by detecting a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or a particular pattern of variants. Preferably, increased levels of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* or increased expression or activity of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide, relative to a control sample, for example, a sample known not to be associated with a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, indicates an increased susceptibility or likelihood that the individual has a cell proliferation disease, an apoptotic disease, or a cell

differentiation disease. Alternatively, decreased levels of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* or decreased expression or activity of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide, relative to a control sample, for example, a sample
5 known not to be associated with a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, indicates a decreased susceptibility or likelihood that the individual has a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

Both quantitative and qualitative alterations can also be present. An
10 “alteration” or “modulation” in the polypeptide expression, activity, or composition, as used herein, refers to an alteration in expression or composition in a test sample, as compared with the expression or composition of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide in a control sample. A control sample is a sample that corresponds to the test sample (*e.g.*, is
15 from the same type of cells), and is from an individual who is not affected by a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. An alteration in the expression or composition of the polypeptide in the test sample, as compared with the control sample, is indicative of a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.
20 Similarly, the presence of one or more different variants in the test sample, or the presence of significantly different amounts of different variants in the test sample, as compared with the control sample, is indicative of a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

It is understood that alterations or modulations in polypeptide expression or
25 function can occur in varying degrees. For example, an alteration or modulation in expression can be an increase, for example, by at least 1.5-fold to 2-fold, at least 3-fold, or, at least 5-fold, relative to the control. Alternatively, the alteration or modulation in polypeptide expression can be a decrease, for example, by at least 10%, at least 40%, 50%, or 75%, or by at least 90%, relative to the control.

30 Various means of examining expression or composition of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide can be used, including spectroscopy, colorimetry, electrophoresis, isoelectric focusing, and

immunoassays (*e.g.*, David *et al.*, U.S. Patent No. 4,376,110) such as immunoblotting (see also Ausubel *et al.*, *supra*; particularly chapter 10). For example, in one embodiment, an antibody capable of binding to the polypeptide (*e.g.*, as described above), preferably an antibody with a detectable label, can be
5 used. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or F(ab')₂) can be used. The term "labeled," with regard to the antibody, is intended to encompass direct labeling of the antibody by coupling (*i.e.*, physically linking) a detectable substance to the antibody, as well as indirect labeling of the antibody by reacting it with another
10 reagent that is directly labeled. An example of indirect labeling is detection of a primary antibody using a fluorescently labeled secondary antibody.

Western blotting analysis, using an antibody as described above that specifically binds to a mutant HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, or an antibody that specifically
15 binds to a non-mutant HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, or an antibody that specifically binds to a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)*, can be used to identify the presence in a test sample of a particular variant of a polypeptide encoded by a polymorphic or mutant *HDAC9*, *HDAC9a*,
20 *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)*, or the absence in a test sample of a particular variant or of a polypeptide encoded by a non-polymorphic or non-mutant gene. The presence of a polypeptide encoded by a polymorphic or mutant gene, or the absence of a polypeptide encoded by a non-polymorphic or non-mutant gene, is diagnostic for a decreased susceptibility to a cell proliferation
25 disease, an apoptotic disease, or a cell differentiation disease, as is the presence (or absence) of particular variants encoded by the *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule.

In one embodiment of this method, the level or amount of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide in a test
30 sample is compared with the level or amount of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide in a control sample. A level or amount of the polypeptide in the test sample that is higher or

lower than the level or amount of the polypeptide in the control sample, such that the difference is statistically significant, is indicative of an alteration in the expression of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, and is diagnostic for a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

Alternatively, the composition of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide in a test sample is compared with the composition of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide in a control sample. A difference in the composition of the polypeptide in the test sample, as compared with the composition of the polypeptide in the control sample (*e.g.*, the presence of different variants), is diagnostic for a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. In another embodiment, both the level or amount and the composition of the polypeptide can be assessed in the test sample and in the control sample. A difference in the amount or level of the polypeptide in the test sample, compared to the control sample; a difference in composition in the test sample, compared to the control sample; or both a difference in the amount or level, and a difference in the composition, is indicative of a decreased susceptibility to a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

Kits (*e.g.*, reagent kits) useful in the methods of diagnosis comprise components useful in any of the methods described herein, including, for example, hybridization probes or primers as described herein (*e.g.*, labeled probes or primers), reagents for detection of labeled molecules, restriction enzymes (*e.g.*, for RFLP analysis), allele-specific oligonucleotides, antibodies that bind to a mutant or to non-mutant (native) HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, means for amplification of nucleic acids comprising HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS), or means for analyzing the nucleic acid sequence of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS), or for analyzing the amino acid sequence of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, etc.

SCREENING ASSAYS AND AGENTS IDENTIFIED THEREBY

The invention provides methods (also referred to herein as “screening assays”) for identifying the presence of a nucleotide that hybridizes to a nucleic acid of the invention, as well as for identifying the presence of a polypeptide encoded by a nucleic acid of the invention. In one embodiment, the presence (or absence) of a nucleic acid molecule of interest (*e.g.*, a nucleic acid that has significant homology with a nucleic acid of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*) in a sample can be assessed by contacting the sample with a nucleic acid comprising a nucleic acid of the invention (*e.g.*, a nucleic acid having the sequence of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, which may optionally comprise at least one polymorphism, or the complement thereof, or a nucleic acid encoding an amino acid having the sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10, or a fragment or variant of such nucleic acids), under stringent conditions as described above, and then assessing the sample for the presence (or absence) of hybridization. In a preferred embodiment, high stringency conditions are conditions appropriate for selective hybridization. In another embodiment, a sample containing the nucleic acid molecule of interest is contacted with a nucleic acid containing a contiguous nucleotide sequence (*e.g.*, a primer or a probe as described above) that is at least partially complementary to a part of the nucleic acid molecule of interest (*e.g.*, an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid), and the contacted sample is assessed for the presence or absence of hybridization. In a preferred embodiment, the nucleic acid containing a contiguous nucleotide sequence is completely complementary to a part of the nucleic acid molecule of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*.

In any of the above embodiments, all or a portion of the nucleic acid of interest can be subjected to amplification prior to performing the hybridization.

In another embodiment, the presence (or absence) of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide, such as a polypeptide of the invention or a fragment or variant thereof, in a sample can be assessed by contacting the sample with an antibody that specifically binds to the

polypeptide of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) (e.g., an antibody such as those described above), and then assessing the sample for the presence (or absence) of binding of the antibody to the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide.

- 5 In another embodiment, the invention provides methods for identifying agents or compounds (e.g., fusion proteins, polypeptides, peptidomimetics, prodrugs, receptors, binding agents, antibodies, small molecules or other drugs, or ribozymes) that alter or modulate (e.g., increase or decrease) the activity of the polypeptides described herein, or that otherwise interact with the polypeptides
- 10 herein. For example, such compounds can be compounds or agents that bind to polypeptides described herein (e.g., HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrates or agents); that have a stimulatory or inhibitory effect on, for example, activity of polypeptides of the invention; or that change (e.g., enhance or inhibit) the ability of the polypeptides of the invention to
- 15 interact with HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) binding agents; or that alter post-translational processing of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide (e.g., agents that alter proteolytic processing to direct the polypeptide from where it is normally synthesized to another location in the cell, such as the cell
- 20 surface; or agents that alter proteolytic processing such that more polypeptide is released from the cell, etc.). In one example, the binding agent is a cell proliferation disease binding agent, an apoptotic disease binding agent, or a cell differentiation disease binding agent. As used herein, by a "cell proliferation disease binding agent," an "apoptotic disease binding agent," or a "cell differentiation disease
- 25 binding agent" is meant an agent as described herein that binds to a polypeptide of the present invention and modulates a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. The modulation can be an increase or a decrease in the severity or progression of the disease. In addition, a cell proliferation disease binding agent, an apoptotic disease binding agent, or a cell differentiation disease
- 30 binding agent includes an agent that binds to a polypeptide that is upstream (earlier) or downstream (later) of the cell signaling events mediated by a polypeptide of the

present invention, and thereby modulates the overall activity of the signaling pathway; in turn, the disease state is modulated.

The candidate compound can cause an increase in the activity of the polypeptide. For example, the activity of the polypeptide can be increased by at least 1.5-fold to 2-fold, at least 3-fold, or, at least 5-fold, relative to the control. Alternatively, the polypeptide activity can be a decrease, for example, by at least 10%, at least 20%, 40%, 50%, or 75%, or by at least 90%, relative to the control.

In one embodiment, the invention provides assays for screening candidate compounds or test agents to identify compounds that bind to or modulate the activity of polypeptides described herein (or biologically active portion(s) thereof), as well as agents identifiable by the assays. As used herein, a "candidate compound" or "test agent" is a chemical molecule, be it naturally-occurring or artificially-derived, and includes, for example, peptides, proteins, synthesized molecules, for example, synthetic organic molecules, naturally-occurring molecule, for example, naturally occurring organic molecules, nucleic acid molecules, and components thereof.

In general, candidate compounds for uses in the present invention may be identified from large libraries of natural products or synthetic (or semi-synthetic) extracts or chemical libraries according to methods known in the art. Those skilled in the field of drug discovery and development will understand that the precise source of test extracts or compounds is not critical to the screening procedure(s) of the invention. Accordingly, virtually any number of chemical extracts or compounds can be screened using the exemplary methods described herein. Examples of such extracts or compounds include, but are not limited to, plant-, fungal-, prokaryotic- or animal-based extracts, fermentation broths, and synthetic compounds, as well as modification of existing compounds. Numerous methods are also available for generating random or directed synthesis (e.g., semi-synthesis or total synthesis) of any number of chemical compounds, including, but not limited to, saccharide-, lipid-, peptide-, and nucleic acid-based compounds. Synthetic compound libraries are commercially available, e.g., from Brandon Associates (Merrimack, NH) and Aldrich Chemical (Milwaukee, WI). Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant, and animal extracts are commercially available from a number of sources, including Biotics (Sussex, UK), Xenova

(Slough, UK), Harbor Branch Oceanographics Institute (Ft. Pierce, FL), and PharmaMar, U.S.A. (Cambridge, MA). In addition, natural and synthetically produced libraries are generated, if desired, according to methods known in the art, e.g., by standard extraction and fractionation methods. For example, candidate
5 compounds can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the "one-bead one-compound" library method; and synthetic library methods using affinity chromatography selection. The biological
10 library approach is limited to polypeptide libraries, while the other four approaches are applicable to polypeptide, non-peptide oligomer or small molecule libraries of compounds (Lam, Anticancer Drug Des., 12: 145 (1997)). Furthermore, if desired, any library or compound is readily modified using standard chemical, physical, or biochemical methods.

15 In addition, those skilled in the art of drug discovery and development readily understand that methods for dereplication (e.g., taxonomic dereplication, biological dereplication, and chemical dereplication, or any combination thereof) or the elimination of replicates or repeats of materials already known for their activities should be employed whenever possible.

20 When a crude extract is found to modulate (i.e., stimulate or inhibit) the expression and/or activity of the nucleic acids and or polypeptides of the present invention, further fractionation of the positive lead extract is necessary to isolate chemical constituents responsible for the observed effect. Thus, the goal of the extraction, fractionation, and purification process is the careful characterization and
25 identification of a chemical entity within the crude extract having an activity that stimulates or inhibits nucleic acid expression, polypeptide expression, or polypeptide biological activity. The same assays described herein for the detection of activities in mixtures of compounds can be used to purify the active component and to test derivatives thereof. Methods of fractionation and purification of such heterogenous
30 extracts are known in the art. If desired, compounds shown to be useful agents for treatment are chemically modified according to methods known in the art. Compounds identified as being of therapeutic value may be subsequently analyzed

using animal models for diseases in which it is desirable to alter the activity or expression of the nucleic acids or polypeptides of the present invention.

In one embodiment, to identify candidate compounds that alter the biological activity, for example, the enzymatic activity or transcriptional repression activity of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, a cell, tissue, cell lysate, tissue lysate, or solution containing or expressing an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide (*e.g.*, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or another variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)*), or a fragment or derivative thereof (as described above), can be contacted with a candidate compound to be tested under conditions suitable for enzymatic reaction or transcriptional repression reaction, as described herein.

Alternatively, the polypeptide can be contacted directly with the candidate compound to be tested. The level (amount) of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) biological activity is assessed (*e.g.*, the level (amount) of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) biological activity is measured, either directly or indirectly), and is compared with the level of biological activity in a control (*i.e.*, the level of activity of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide or active fragment or derivative thereof in the absence of the candidate compound to be tested, or in the presence of the candidate compound vehicle only). If the level of the biological activity in the presence of the candidate compound differs, by an amount that is statistically significant, from the level of the biological activity in the absence of the candidate compound, or in the presence of the candidate compound vehicle only, then the candidate compound is a compound that alters the biological activity of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide. For example, an increase in the level of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) enzymatic or transcriptional repression activity relative to a control, indicates that the candidate compound is a compound that enhances (is an agonist of) HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) activity. Similarly,

a decrease in the enzymatic level or transcriptional repression level of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) activity relative to a control, indicates that the candidate compound is a compound that inhibits (is an antagonist of) HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) activity. In another embodiment, the level of biological activity of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide or derivative or fragment thereof in the presence of the candidate compound to be tested, is compared with a control level that has previously been established. A level of the biological activity in the presence of the candidate compound that differs from the control level by an amount that is statistically significant indicates that the compound alters HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) biological activity.

The present invention also relates to an assay for identifying compounds that alter the expression of an *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or HDRP(Δ NLS) nucleic acid molecule (e.g., antisense nucleic acids, fusion proteins, polypeptides, peptidomimetics, prodrugs, receptors, binding agents, antibodies, small molecules or other drugs, or ribozymes) that alter (e.g., increase or decrease) expression (e.g., transcription or translation) of the nucleic acid molecule or that otherwise interact with the nucleic acids described herein, as well as compounds identifiable by the assays. For example, a solution containing a nucleic acid encoding an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide can be contacted with a candidate compound to be tested. The solution can comprise, for example, cells containing the nucleic acid or cell lysate containing the nucleic acid; alternatively, the solution can be another solution that comprises elements necessary for transcription/translation of the nucleic acid. Cells not suspended in solution can also be employed, if desired. The level and/or pattern of *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or HDRP(Δ NLS) expression (e.g., the level and/or pattern of mRNA or of protein expressed, such as the level and/or pattern of different variants) is assessed, and is compared with the level and/or pattern of expression in a control (i.e., the level and/or pattern of *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or HDRP(Δ NLS) expression in the absence of the candidate compound, or in the presence of the candidate,

compound vehicle only). If the level and/or pattern in the presence of the candidate compound differs, by an amount or in a manner that is statistically significant, from the level and/or pattern in the absence of the candidate compound, or in the presence of the candidate compound vehicle only, then the candidate compound is a

5 compound that alters the expression of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. Enhancement of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression indicates that the candidate compound is an agonist of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* activity. Similarly, inhibition of *HDAC9*,

10 *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression indicates that the candidate compound is an antagonist of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* activity. In another embodiment, the level and/or pattern of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide(s) (e.g., different variants) in the presence of the

15 candidate compound to be tested, is compared with a control level and/or pattern that has previously been established. A level and/or pattern in the presence of the candidate compound that differs from the control level and/or pattern by an amount or in a manner that is statistically significant indicates that the candidate compound alters *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*

20 expression.

In another embodiment of the invention, compounds that alter the expression of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule or that otherwise interact with the nucleic acids described herein, can be identified using a cell, cell lysate, or solution containing a nucleic

25 acid encoding the promoter region of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* gene operably linked to a reporter gene. After contact with a candidate compound to be tested, the level of expression of the reporter gene (e.g., the level of mRNA or of protein expressed) is assessed, and is compared with the level of expression in a control (i.e., the level of the expression

30 of the reporter gene in the absence of the candidate compound, or in the presence of the candidate compound vehicle only). If the level in the presence of the candidate compound differs, by an amount or in a manner that is statistically significant, from

the level in the absence of the candidate compound, or in the presence of the candidate compound vehicle only, then the candidate compound is a compound that alters the expression of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, as indicated by its ability to alter expression of a gene that is

5 operably linked to the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* gene promoter. Enhancement of the expression of the reporter indicates that the compound is an agonist of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* activity. Similarly, inhibition of the expression of the reporter indicates that the compound is an antagonist of *HDAC9*, *HDAC9a*,

10 *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* activity. In another embodiment, the level of expression of the reporter in the presence of the candidate compound to be tested, is compared with a control level that has previously been established. A level in the presence of the candidate compound that differs from the control level by an amount or in a manner that is statistically significant indicates

15 that the candidate compound alters *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression.

Compounds that alter the amounts of different variants encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (e.g., a compound that enhances activity of a first variant, and that inhibits activity of a second variant),

20 as well as compounds that are agonists of activity of a first variant and antagonists of activity of a second variant, can easily be identified using these methods described above.

In other embodiments of the invention, assays can be used to assess the impact of a candidate compound on the activity of a polypeptide in relation to an

25 *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* substrate, for example, an inhibitor of histone deacetylase activity. These inhibitors fall into four general classes: 1) short-chain fatty acids (e.g., 4-phenylbutyrate and valproic acid); 2) hydroxamic acids (e.g., SAHA, Pyroxamide, trichostatin A (TSA), oxamflatin and CHAPs, such as, CHAP1 and CHAP 31); 3) cyclic tetrapeptides

30 (Trapoxin A, Apicidin and Depsipeptide (FK-228, also known as FR9011228); 4) benzamides (e.g., MS-275); and other compounds such as Scriptaid. Examples of such assays and compounds can be found in U.S. Patent Nos. 5,369,108, issued on

November 29, 1994, 5,700,811, issued on December 23, 1997, and 5,773,474, issued on June 30, 1998 to Breslow *et al.*, U.S. Patent Nos. 5,055,608, issued on October 8, 1991, and 5,175,191, issued on December 29, 1992 to Marks *et al.*, as well as, Yoshida *et al.*, *supra*; Saito *et al.*, *supra*; Furamai *et al.*, *supra*; Komatsu *et al.*, *supra*; Su *et al.*, *supra*; Lee *et al.*, *supra* and Suzuki *et al.* *supra*, the entire content of all of which are hereby incorporated by reference.

In one example, a cell or tissue that expresses or contains a compound that interacts with HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) (herein referred to as an "HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate," which can be a polypeptide or other molecule that interacts with HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS)) is contacted with HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) in the presence of a candidate compound, and the ability of the candidate compound to alter the interaction between HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) and the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP (Δ NLS) substrate is determined, for example, by assaying activity of the polypeptide. Alternatively, a cell lysate or a solution containing the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate, can be used. A compound that binds to HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) or the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate can alter the interaction by interfering with, or enhancing the ability of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) to bind to, associate with, or otherwise interact with the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate.

Determining the ability of the candidate compound to bind to HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) or an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate can be accomplished, for example, by coupling the candidate compound with a radioisotope or enzymatic label such that binding of the candidate compound to the polypeptide can be determined by detecting the labeled with ^{125}I , ^{35}S , ^{14}C , or ^3H , either directly or indirectly, and the radioisotope detected by direct counting of

radioemmission or by scintillation counting. Alternatively, candidate compound can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

- 5 It is also within the scope of this invention to determine the ability of a candidate compound to interact with the polypeptide without the labeling of any of the interactants. For example, a microphysiometer can be used to detect the interaction of a candidate compound with HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) or an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate without the labeling of either the candidate compound, HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS), or the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate (McConnell *et al.*, (1992) Science, 257: 1906-1912). As used herein, a "microphysiometer" (*e.g.*, CYTOSENSOR™) is an analytical
- 10 instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between ligand and polypeptide.

- In another embodiment of the invention, assays can be used to identify polypeptides that interact with one or more HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptides, as described herein. For example, a yeast two-hybrid system such as that described by Fields and Song (Fields and Song, Nature 340: 245-246 (1989)) can be used to identify polypeptides that interact with one or more HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptides. In such a yeast two-hybrid system, vectors are
- 20 constructed based on the flexibility of a transcription factor that has two functional domains (a DNA binding domain and a transcription activation domain). If the two domains are separated but fused to two different proteins that interact with one another, transcriptional activation can be achieved, and transcription of specific markers (*e.g.*, nutritional markers such as His and Ade, or color markers such as lacZ) can be used to identify the presence of interaction and transcriptional
- 25 activation. For example, in the methods of the invention, a first vector is used that includes a nucleic acid encoding a DNA binding domain and an HDAC9, HDAC9a,
- 30

HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, variant, or fragment or derivative thereof, and a second vector is used that includes a nucleic acid encoding a transcription activation domain and a nucleic acid encoding a polypeptide that potentially may interact with the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, variant, or fragment or derivative thereof (*e.g.*, an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide substrate or receptor). Incubation of yeast containing the first vector and the second vector under appropriate conditions (*e.g.*, mating conditions such as used in the MATCHMAKER™ system from Clontech) allows identification of colonies that express the markers of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS). These colonies can be examined to identify the polypeptide(s) that interact with the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide or fragment or derivative thereof. Such polypeptides may be useful as compounds that alter the activity or expression of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, as described above.

In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, or an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate, or other components of the assay on a solid support, in order to facilitate separation of complexed from uncomplexed forms of one or both of the polypeptides, as well as to accommodate automation of the assay. Binding of a candidate compound to the polypeptide, or interaction of the polypeptide with a substrate in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein (*e.g.*, a glutathione-S-transferase fusion protein) can be provided that adds a domain that allows HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) or an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) substrate to be bound to a matrix or other solid support.

In another embodiment, modulators of expression of nucleic acid molecules of the invention are identified in a method wherein a cell, cell lysate, tissue, tissue lysate, or solution containing a nucleic acid encoding HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) is contacted with a candidate compound and the expression of appropriate mRNA or polypeptide (*e.g.*, variant(s)) in the cell, cell lysate, tissue, or tissue lysate, or solution, is determined. The level of expression of appropriate mRNA or polypeptide(s) in the presence of the candidate compound is compared to the level of expression of mRNA or polypeptide(s) in the absence of the candidate compound, or in the presence of the candidate compound vehicle only. The candidate compound can then be identified as a modulator of expression based on this comparison. For example, when expression of mRNA or polypeptide is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator or enhancer of the mRNA or polypeptide expression. Alternatively, when expression of the mRNA or polypeptide is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of the mRNA or polypeptide expression. The level of mRNA or polypeptide expression in the cells can be determined by methods described herein for detecting mRNA or polypeptide.

This invention further pertains to novel compounds identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use a compound identified as described herein in an appropriate animal model. For example, a compound identified as described herein (*e.g.*, a candidate compound that is a modulating compound such as an antisense nucleic acid molecule, a specific antibody, or a polypeptide substrate) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such a compound. Alternatively, a compound identified as described herein can be used in an animal model to determine the mechanism of action of such a compound. Furthermore, this invention pertains to uses of novel compounds identified by the above-described screening assays for treatments as described herein. In addition, a compound identified as described herein can be used to alter activity of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, or to

alter expression of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, by contacting the polypeptide or the nucleic acid molecule (or contacting a cell comprising the polypeptide or the nucleic acid molecule) with the compound identified as described herein.

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PHARMACEUTICAL COMPOSITIONS

The present invention also pertains to pharmaceutical compositions comprising nucleic acids described herein, particularly nucleotides encoding the polypeptides described herein; comprising polypeptides described herein (*e.g.*, SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, and/or other variants encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*); and/or comprising a compound that alters (*e.g.*, increases or decreases) *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression or *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide activity as described herein. For instance, a polypeptide, protein, fragment, fusion protein or prodrug thereof, or a nucleotide or nucleic acid construct (vector) comprising a nucleotide of the present invention, a compound that alters *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide activity, a compound that alters *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid expression, or an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* substrate or binding partner, can be formulated with a physiologically acceptable carrier or excipient to prepare a pharmaceutical composition. The carrier and composition can be sterile. The formulation should suit the mode of administration.

Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions (*e.g.*, NaCl), saline, buffered saline, alcohols, glycerol, ethanol, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose, amylose or starch, dextrose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrrolidone, etc., as well as combinations thereof. The pharmaceutical preparations can, if desired, be mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic

pressure, buffers, coloring, flavoring and/or aromatic substances and the like that do not deleteriously react with the active compounds.

The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. The composition can be a liquid
5 solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, polyvinyl pyrrolidone, sodium saccharine, cellulose, magnesium carbonate,
10 etc.

Methods of introduction of these compositions include, but are not limited to, intradermal, intramuscular, intraperitoneal, intraocular, intravenous, subcutaneous, topical, oral and intranasal. Other suitable methods of introduction can also include gene therapy (as described below), rechargeable or biodegradable
15 devices, particle acceleration devices ("gene guns") and slow release polymeric devices. The pharmaceutical compositions of this invention can also be administered as part of a combinatorial therapy with other compounds.

The composition can be formulated in accordance with the routine procedures as a pharmaceutical composition adapted for administration to human
20 beings. For example, compositions for intravenous administration typically are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free
25 concentrate in a hermetically sealed container such as an ampule or sachette indicating the quantity of active compound. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water, saline or dextrose/water. Where the composition is administered by injection, an ampule of sterile water for injection or saline can be
30 provided so that the ingredients may be mixed prior to administration.

For topical application, nonsprayable forms, viscous to semi-solid or solid forms comprising a carrier compatible with topical application and having a

dynamic viscosity preferably greater than water, can be employed. Suitable formulations include but are not limited to solutions, suspensions, emulsions, creams, ointments, powders, enemas, lotions, sols, liniments, salves, aerosols, etc., that are, if desired, sterilized or mixed with auxiliary agents, *e.g.*, preservatives, stabilizers, wetting agents, buffers or salts for influencing osmotic pressure, etc. The compound may be incorporated into a cosmetic formulation. For topical application, also suitable are sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier material, is packaged in a squeeze bottle or in admixture with a pressurized volatile, normally gaseous propellant, *e.g.*, pressurized air.

Compounds described herein can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The compounds are administered in a therapeutically effective amount. The amount of compounds that will be therapeutically effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the symptoms of a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, and should be decided according to the judgment of a practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, that notice

reflects approval by the agency of manufacture, use of sale for human administration. The pack or kit can be labeled with information regarding mode of administration, sequence of drug administration (*e.g.*, separately, sequentially or concurrently), or the like. The pack or kit may also include means for reminding the patient to take the therapy. The pack or kit can be a single unit dosage of the combination therapy or it can be a plurality of unit dosages. In particular, the compounds can be separated, mixed together in any combination, present in a single vial or tablet. Compounds assembled in a blister pack or other dispensing means is preferred. For the purpose of this invention, unit dosage is intended to mean a dosage that is dependent on the individual pharmacodynamics of each compound and administered in FDA approved dosages in standard time courses.

METHODS OF THERAPY

The present invention also pertains to methods of treatment (prophylactic, diagnostic, and/or therapeutic) for a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, using an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) therapeutic compound. An "HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) therapeutic compound" is a compound that alters (*e.g.*, enhances or inhibits) HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide activity and/or *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule expression, as described herein (*e.g.*, an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) agonist or antagonist). HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) therapeutic compounds can alter HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide activity or nucleic acid molecule expression by a variety of means, such as, for example, by providing additional HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide or by upregulating the transcription or translation of the *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule; by altering post-translational processing of the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide; by altering

transcription of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* variants; or by interfering with *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide activity (e.g., by binding to an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide), or by downregulating the transcription or translation of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid molecule. Representative *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* therapeutic compounds include the following: nucleic acids or fragments or derivatives thereof described herein, particularly nucleotides encoding the polypeptides described herein and vectors comprising such nucleic acids (e.g., a nucleic acid molecule, cDNA, and/or RNA, such as a nucleic acid encoding an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide or active fragment or derivative thereof, or an oligonucleotide; for example, SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, which may optionally comprise at least one polymorphism, or a nucleic acid encoding SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, or fragments or derivatives thereof); polypeptides described herein (e.g., SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10 and/or other variants encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, or fragments or derivatives thereof); *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* substrates; peptidomimetics; fusion proteins or prodrugs thereof; antibodies (e.g., an antibody to a mutant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide, or an antibody to a non-mutant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide, or an antibody to a particular variant encoded by *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*, as described above); ribozymes; other small molecules; and other compounds that alter (e.g., enhance or inhibit) *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid expression or polypeptide activity, for example, those compounds identified in the screening methods described herein, or that regulate transcription of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* variants (e.g.,

compounds that affect which variants are expressed, or that affect the amount of each variant that is expressed. More than one HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) therapeutic compound can be used concurrently, if desired.

- 5 The HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) therapeutic compound that is a nucleic acid is used in the treatment of a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. The term, "treatment" as used herein, refers not only to ameliorating symptoms associated with the disease, but also preventing or delaying the onset of the disease,
- 10 and also lessening the severity or frequency of symptoms of the disease. The therapy is designed to alter (*e.g.*, inhibit or enhance), replace or supplement activity of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide in an individual. For example, an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) therapeutic compound can be administered in
- 15 order to upregulate or increase the expression or availability of the *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule or of specific variants of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS), or, conversely, to downregulate or decrease the expression or availability of the *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or
- 20 *HDRP(Δ NLS)* nucleic acid molecule or specific variants of HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS). Upregulation or increasing expression or availability of a native *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule or of a particular variant could interfere with or compensate for the expression or activity of a defective gene
- 25 or another variant; downregulation or decreasing expression or availability of a native *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule or of a particular variant could minimize the expression or activity of a defective gene or the particular variant and thereby minimize the impact of the defective gene or the particular variant.

- 30 The HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) therapeutic compound(s) are administered in a therapeutically effective amount (*i.e.*, an amount that is sufficient to treat the disease, such as by

ameliorating symptoms associated with the disease, preventing or delaying the onset of the disease, and/or also lessening the severity or frequency of symptoms of the disease). The amount that will be therapeutically effective in the treatment of a particular individual's disorder or condition will depend on the symptoms and severity of the disease, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of a practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

In one embodiment, a nucleic acid of the invention (*e.g.*, a nucleic acid encoding an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, such as SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, which may optionally comprise at least one polymorphism, or a nucleic acid that encodes an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide or a variant, derivative or fragment thereof, such as a nucleic acid encoding the protein of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10) can be used, either alone or in a pharmaceutical composition as described above. For example, HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) or a cDNA encoding an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, either by itself or included within a vector, can be introduced into cells (either *in vitro* or *in vivo*) such that the cells produce native HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide. If desired, cells that have been transformed with the gene or cDNA or a vector comprising the gene or cDNA can be introduced (or re-introduced) into an individual affected with the disease. Thus, cells that, in nature, lack native HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) expression and activity, or have mutant HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) expression and activity, or have expression of a disease-associated HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) variant,

- can be engineered to express an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide or an active fragment of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide (or a different variant of an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide). In a preferred embodiment, nucleic acid encoding the HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide, or an active fragment or derivative thereof, can be introduced into an expression vector, such as a viral vector, and the vector can be introduced into appropriate cells in an animal. Other gene transfer systems, including viral and nonviral transfer systems, can be used. Alternatively, nonviral gene transfer methods, such as calcium phosphate coprecipitation, mechanical techniques (*e.g.*, microinjection); membrane fusion-mediated transfer via liposomes; or direct DNA uptake, can also be used to introduce the desired nucleic acid molecule into a cell.
- Alternatively, in another embodiment of the invention, a nucleic acid of the invention; a nucleic acid complementary to a nucleic acid of the invention; or a portion of such a nucleic acid (*e.g.*, an oligonucleotide as described below), can be used in "antisense" therapy, in which a nucleic acid (*e.g.*, an oligonucleotide) that specifically hybridizes to the RNA and/or genomic DNA of *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* is administered or generated *in situ*. The antisense nucleic acid that specifically hybridizes to the RNA and/or DNA inhibits expression of the *HDAC9*, *HDAC9a*, *HDAC9(Δ NLS)*, *HDAC9a(Δ NLS)*, or *HDRP(Δ NLS)* nucleic acid molecule, *e.g.*, by inhibiting translation and/or transcription. Binding of the antisense nucleic acid can be by conventional base pair complementarity, or, for example, in the case of binding to DNA duplexes, through specific interaction in the major groove of the double helix.

An antisense construct of the present invention can be delivered, for example, as an expression plasmid as described above. When the plasmid is transcribed in the cell, it produces RNA that is complementary to a portion of the mRNA and/or DNA that encodes an HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide. Alternatively, the antisense construct can be an oligonucleotide probe which is generated *ex vivo* and introduced

into cells; it then inhibits expression by hybridizing with the mRNA and/or genomic DNA of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*. In one embodiment, the oligonucleotide probes are modified oligonucleotides that are resistant to endogenous nucleases, *e.g.* exonucleases and/or endonucleases, thereby rendering them stable *in vivo*. Exemplary nucleic acid molecules for use as antisense oligonucleotides are phosphoramidate, phosphothioate and methylphosphonate analogs of DNA (see also U.S. Patent Nos. 5,176,996; 5,264,564; and 5,256,775). Additionally, general approaches to constructing oligomers useful in antisense therapy are also described, for example, by Van der Krol *et al.*, *Biotechniques* 6: 958-976 (1988); and Stein *et al.*, *Cancer Res* 48: 2659-2668 (1988). With respect to antisense DNA, oligodeoxyribonucleotides derived from the translation initiation site, *e.g.* between the -10 and +10 regions of an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid sequence, are preferred.

To perform antisense therapy, oligonucleotides (RNA, cDNA or DNA) are designed that are complementary to mRNA encoding an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* polypeptide. The antisense oligonucleotides bind to *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* mRNA transcripts and prevent translation. Absolute complementarity, although preferred, is not required. A sequence "complementary" to a portion of an RNA, as referred to herein, indicates that a sequence has sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double-stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid, as described in detail above. Generally, the longer the hybridizing nucleic acid, the more base mismatches with an RNA it may contain and still form a stable duplex (or triplex, as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures.

The oligonucleotides used in antisense therapy can be DNA, RNA, or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotides can be modified at the base moiety, sugar

moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotides can include other appended groups such as peptides (*e.g.* for targeting host cell receptors *in vivo*), or compounds facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.*, Proc. Natl. Acad. Sci. USA 86: 6553-6556 (1989); Lemaitre *et al.*, Proc. Natl. Acad. Sci. USA 84: 648-652 (1987); PCT International Publication No. W088/09810)) or the blood-brain barrier (see, *e.g.*, PCT International Publication No. W089/10134), or hybridization-triggered cleavage agents (see, *e.g.*, Krol *et al.*, BioTechniques 6: 958-976 (1988)) or intercalating agents. (See, *e.g.*, Zon, Pharm. Res. 5: 539-549 (1988)). To this end, the oligonucleotide may be conjugated to another molecule (*e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent).

The antisense molecules are delivered to cells that express *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* *in vivo*. A number of methods can be used for delivering antisense DNA or RNA to cells; *e.g.*, antisense molecules can be injected directly into the tissue site, or modified antisense molecules, designed to target the desired cells (*e.g.*, antisense linked to peptides or antibodies that specifically bind receptors or antigens expressed on the target cell surface) can be administered systematically. Alternatively, in a preferred embodiment, a recombinant DNA construct is utilized in which the antisense oligonucleotide is placed under the control of a strong promoter (*e.g.*, pol III or pol II). The use of such a construct to transfect target cells in the patient results in the transcription of sufficient amounts of single stranded RNAs that will form complementary base pairs with the endogenous *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* transcripts and thereby prevent translation of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* mRNA. For example, a vector can be introduced *in vivo* such that it is taken up by a cell and directs the transcription of an antisense RNA. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art and described above. For example, a plasmid, cosmid, YAC, or viral vector can be used to prepare the recombinant DNA

construct that can be introduced directly into the tissue site. Alternatively, viral vectors can be used that selectively infect the desired tissue, in which case administration may be accomplished by another route (*e.g.*, systemically).

Endogenous *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or
5 *HDRP(ΔNLS)* expression can also be reduced by inactivating or “knocking out”
HDAC9, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* nucleic acid
sequences or their promoters using targeted homologous recombination (*e.g.*, see
Smithies *et al.*, Nature 317: 230-234 (1985); Thomas and Capecchi, Cell 51:
503-512 (1987); Thompson *et al.*, Cell 5: 313-321 (1989)). For example, a mutant,
10 non-functional *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or
HDRP(ΔNLS) (or a completely unrelated DNA sequence) flanked by DNA
homologous to the endogenous *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*,
HDAC9a(ΔNLS), or *HDRP(ΔNLS)* (either the coding regions or regulatory regions
of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*) can be
15 used, with or without a selectable marker and/or a negative selectable marker, to
transfect cells that express *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or
HDRP(ΔNLS) *in vivo*. Insertion of the DNA construct, via targeted homologous
recombination, results in inactivation of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*,
HDAC9a(ΔNLS), or *HDRP(ΔNLS)*. The recombinant DNA constructs can be
20 directly administered or targeted to the required site *in vivo* using appropriate
vectors, as described above. Alternatively, expression of non-mutant *HDAC9*,
HDAC9a, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* can be increased
using a similar method: Targeted homologous recombination can be used to insert a
DNA construct comprising a non-mutant, functional *HDAC9*, *HDAC9a*,
25 *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (*e.g.*, a gene having SEQ ID
NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9, which
may optionally comprise at least one polymorphism), or a portion thereof, in place
of a mutant *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)*
in the cell, as described above. In another embodiment, targeted homologous
30 recombination can be used to insert a DNA construct comprising a nucleic acid that
encodes an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or
HDRP(ΔNLS) polypeptide variant that differs from that present in the cell.

Alternatively, endogenous *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* expression can be reduced by targeting deoxyribonucleotide sequences complementary to the regulatory region of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* (i.e., the *HDAC9*,
5 *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* promoter and/or enhancers) to form triple helical structures that prevent transcription of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* in target cells in the body. (See generally, Helene Anticancer Drug Des., 6(6): 569-84 (1991); Helene *et al.*, Ann. N.Y. Acad. Sci., 660: 27-36 (1992); and Maher, Bioassays 14(12): 807-15
10 (1992)). Likewise, the antisense constructs described herein, by antagonizing the normal biological activity of one of the *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* proteins, can be used in the manipulation of tissue, e.g., tissue differentiation, both *in vivo* and for *ex vivo* tissue cultures. Furthermore, the antisense techniques (e.g., microinjection of antisense molecules,
15 or transfection with plasmids whose transcripts are anti-sense with regard to an *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* mRNA or gene sequence) can be used to investigate role of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* in developmental events, as well as the normal cellular function of *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*,
20 *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* in adult tissue. Such techniques can be utilized in cell culture, but can also be used in the creation of transgenic animals.

In yet another embodiment of the invention, other *HDAC9*, *HDAC9a*, *HDAC9(ΔNLS)*, *HDAC9a(ΔNLS)*, or *HDRP(ΔNLS)* therapeutic compounds as described herein can also be used in the treatment or prevention of a cell
25 proliferation disease, an apoptotic disease, or a cell differentiation disease. The therapeutic compounds can be delivered in a composition, as described above, or by themselves. They can be administered systemically, or can be targeted to a particular tissue. The therapeutic compounds can be produced by a variety of means, including chemical synthesis; recombinant production; *in vivo* production
30 (e.g., a transgenic animal, such as U.S. Patent No. 4,873,316 to Meade *et al.*), for example, and can be isolated using standard means such as those described herein.

A combination of any of the above methods of treatment (*e.g.*, administration of non-mutant HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), or HDRP(Δ NLS) polypeptide in conjunction with antisense therapy targeting mutant *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or HDRP(Δ NLS) mRNA; administration of a first variant encoded by *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or HDRP(Δ NLS) in conjunction with antisense therapy targeting a second encoded by *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or HDRP(Δ NLS), can also be used.

In another embodiment, the invention is directed to *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or HDRP(Δ NLS) nucleic acid molecules and *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or HDRP(Δ NLS) polypeptides for use as a medicament in therapy. For example, the nucleic acid molecules or polypeptides of the present invention can be used in the treatment of a cell proliferation disease, an apoptotic disease, or a cell differentiation disease. In addition, the *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or HDRP(Δ NLS) nucleic acid molecules and *HDAC9*, *HDAC9a*, *HDAC9*(Δ NLS), *HDAC9a*(Δ NLS), or HDRP(Δ NLS) polypeptides described herein can be used in the manufacture of a medicament for the treatment of a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.

The invention will be further described by the following non-limiting examples. The teachings of all publications cited herein are incorporated herein by reference in their entirety.

EXEMPLIFICATION

Cloning of cDNA encodes a novel HDAC, designated HDAC9

HDAC9 was cloned by PCR and 3' rapid amplification of cDNA ends using primers designed from the sequence of human chromosome 7 whose translated product exhibited 80% identity to the HDAC domain of HDAC4, described in detail as follows.

Database analyses indicate that *HDRP* is located on chromosome 7 (7p15-p21). The human genome database (February 2001 release) of GenBank was searched using the human HDAC4 amino acid sequence. The TBLASTN program

was used to identify open reading frames downstream of *HDRP* on chromosome 7 that exhibit significant homology to the HDAC domain of HDAC4. Several fragments whose translated products exhibit over 58% identity were retrieved. Two sense primers (OL486, 5'-CCATGGAAACGGTACCCAGCAGGC-3' (SEQ ID NO: 16) and OL487, 5'-CACTCCATCGCTATGATGAAGGG-3' (SEQ ID NO: 17)) and antisense primers (OL484, 5'-AGTTCCTTCATCATAGCGATGG-3' (SEQ ID NO: 18) and OL485, 5'-AATGTACAGGATGCTGGGGT-3' (SEQ ID NO: 19)) each were designed based upon one of these fragments whose translated products matched amino acids 842-873 of HDAC4. RT-PCR was performed using each of the antisense primers and a sense primer (5'-CCCTTG TAGCTGGTGGAGTTCCTT-3' (SEQ ID NO: 20)) from the coding region of *HDRP* and human brain cDNA as a template. PCR was performed in a Biometra TGRADIENT Thermocycler for 30 cycles at 95°C for 20 seconds, 60°C for 20 seconds, and 72°C for 120 seconds.

3'-rapid amplification of cDNA ends was performed using the sense primer OL486 and adaptor primer 1 (Clontech), and marathon-ready cDNA from human brain (Clontech, Palo Alto, CA) according to the manufacturer's instruction. The products were re-amplified using nested sense primer OL487 and adaptor primer 2 (Clontech, Palo Alto, CA). PCR products were cloned into pGEM-T-easy vector (Promega, Madison, WI) and sequenced using an automated DNA sequencer at the DNA Sequencing Core Facility of the Memorial Sloan-Kettering Cancer Center, using DNA sequencing methods known to one of skill in the art.

Two cDNAs were cloned from the above-described methods. One cDNA (SEQ ID NO:1) encodes an HDAC9 protein that is 1011 amino acids in length. The other cDNA (SEQ ID NO: 3) encodes an HDAC9a protein that is 879 amino acids long. The cDNA sequence and amino sequence of *HDAC9* and *HDAC9a* are shown in FIGS. 1A-1G and FIGS. 2A-2B, respectively. Database analyses of these cDNAs against human genomic DNA sequences indicated that these two cDNAs are generated by alternatively splicing. An alignment of HDAC9, HDAC9a, *HDRP*, and HDAC4 is shown in FIGS. 3A-3C.

Each of the HDAC9 and HDAC9a nucleic acid sequences were cloned into the pFLAG-CMV-5b vector (Sigma) in frame with the C-terminal FLAG tag. Only

the coding regions plus three extra base pairs (ACC) of cDNA of the HDAC9 and HDAC9a nucleic acid sequences were included in the constructs. These constructs are referred to herein as HDAC9-FLAG and HDAC9a-FLAG, respectively. These constructs are contained in *E. coli*, and can readily be expressed. For HDAC9, the
5 insert is 3033 bp and for HDAC9a, the insert size is 2637 bp. Both HDAC9 and HDAC9a can be released with EcoRV and BamHI (whose sites have been incorporated in the primers to obtain HDAC9 and HDAC9a coding cDNA for cloning purpose) restriction enzyme digestion.

The *HDAC9* cDNA sequences from the known 5'-end of *HDRP* cDNA to the
10 3'-untranslated region cloned in this study cover over 511 kb of genomic DNA on chromosome 7. As shown in FIG. 4, the coding region cDNA of *HDAC9* resides in 23 exons spanning 458 kb of genomic sequence. Exons 21, 22, and 23 are one single exon in HDAC9a, but the middle exon that is numbered exon 22 in FIG. 4, containing an in-frame stop codon, is spliced out in HDAC9. In addition, exons 12
15 and 13 are a single exon used by HDRP. Exon 13 is spliced as part of an intron in HDAC9 and HDAC9a.

Further analysis revealed that exon 7, which contains a nuclear localization signal (NLS) is alternatively spliced in an HDRP isoform, creating HDRP(Δ NLS). RT-PCR analyses using primers based on sequences from exon 6 and exon 14
20 indicate that this alternative splicing event also occurs in *HDAC9* and/or *HDAC9a*. Thus, it is possible that at least 6 proteins can be generated from a single *HDAC9* gene by alternatively splicing of its RNA. The cDNA sequences and amino acid sequences for HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS) are shown in FIGS. 1A-1O and 2A-2E, respectively.

25

HDAC9 mRNA is differentially expressed among human tissues

The expression of *HDAC9* mRNA was determined by Northern blot analysis using a human multiple tissue Northern blot (Clontech, Palo Alto, CA). Hybridization was performed according to the manufacturer's instruction using
30 ExPressHyb solution (Clontech, Palo Alto, CA). The ³²P-random priming labeled 3'-untranslated region common to both *HDAC9* and *HDAC9a* that shares no significant sequence homology with *HDRP* was used as a probe. Two transcripts at

9.8 and 4.1 kb were detected in all tissues examined (FIG. 6A). The 4.1 kb transcript is shorter than the 4.4 kb *HDRP* transcript (See Zhou, *et al.*, Proc. Natl. Acad. Sci. USA, 97:1056-1061 (2000)). A third transcript at 1.2 kb was detected in placenta (FIG. 6A). Similar to *HDRP* (See Zhou, X., *et al.*, Proc. Natl. Acad. Sci. USA, 97:1056-1061 (2000)), high levels of *HDAC9* transcripts were detected in brain and skeletal muscle (FIG. 6A).

The distribution of alternatively spliced mRNA variants among tissues was examined by RT-PCR using primers (OL516 5'-TGTGTCATCGAGCTGGCTTC-3' (SEQ ID NO: 21) and OL517 5'-ATCTTCTGCAAGTGGCTCCA-3' (SEQ ID NO: 22)) spanning the alternatively spliced exon 22 and cDNA panel from the same tissues as the multiple tissue Northern blot. PCR was performed in a Biometra TGRADIENT Thermocycler for 30 cycles at 95°C for 20 seconds, 60°C for 20 seconds, and 72°C for 60 seconds. The expected sizes of PCR products were 680 base pairs for *HDAC9* and 993 base pairs for *HDAC9a*. The ratio of *HDAC9* and *HDAC9a* transcripts differed among tissues (FIG. 6B). In the placenta and kidney, the levels of the two transcripts were about the same (FIG. 6B). In the brain, heart, and pancreas, there were more transcripts of *HDAC9* than *HDAC9a*. In the other tissues examined, there were more *HDAC9a* transcripts than *HDAC9* transcripts (FIG. 6B). Under the conditions tested, *HDAC9* transcripts were undetectable in liver (FIG. 6B). The lung had an *HDAC9* product that was larger than expected and abundant. The lung also had low levels of *HDAC9* transcripts and *HDAC9a* transcripts (FIG. 6B). An additional PCR product was also amplified from cDNA of the pancreas; this product was than the expected products from *HDAC9* and *HDAC9a* (FIG. 6B). The identity of the different sized transcripts is unknown.

25

HDAC9 and HDAC9a possess histone deacetylase activity

HDAC9 was named based on sequence homology to *HDAC4* (FIGS. 3A-3C). To determine whether *HDAC9* and *HDAC9a* possess HDAC activity, an HDAC enzymatic assay was performed using anti-FLAG immunoprecipitated *HDAC9*-FLAG and *HDAC9a*-FLAG.

30

C-terminal FLAG-tagged *HDAC9* (*HDAC9*-FLAG) and *HDAC9a* (*HDAC9a*-FLAG) expression vectors were constructed using the pFLAG-CMV-5b

vector (Sigma) and PCR amplified coding regions of HDAC9 and HDAC9a in frame with the FLAG-tag to form pFLAG-CMV-5b-HDAC9 (plasmid VR1) and pFLAG-CMV-5b-HDAC9a (plasmid VR2). All constructs were confirmed by DNA sequencing.

- 5 Transfection of human kidney 293T cells, immunoprecipitation using anti-FLAG M2 Agarose (Sigma), Western blot analyses and dual luciferase assays were performed essentially as previously described by Zhou *et al.* (Proc. Natl. Acad. Sci. USA, 97:1056-1061 (2000)). Briefly, the cells (American Type Culture Collection) were cultured in DME HG medium (GIBCO/BRL) supplemented with 10%
10 (vol/vol) FBS at 37 °C in a 5% CO₂ atmosphere. Transient transfection was performed by using Lipofectamine (GIBCO/BRL) or Fugene 6 (Roche Molecular Biochemicals) according to the manufacturers' instructions. Cells were harvested 24 to 48 hours after transfection and lysed in IP lysis buffer (50 mM Tris·HCl, pH 7.5/120 mM NaCl/5 mM EDTA/0.5% NP-40) at 5 x 10⁷ cells per ml.
15 Immunoprecipitation with anti-FLAG M2-agarose (Sigma, St. Louis, MO) was performed according to the manufacturer's instructions. Immunoprecipitated proteins were released from the agarose beads by using FLAG-peptide and either used directly for HDAC enzymatic activity assays or resolved on SDS/PAGE for Western blot analyses. Anti-FLAG antibody was purchased from Sigma (St. Louis,
20 MO). Western blot analyses were performed using standard methods.

- HDAC9 and HDAC9a enzymatic activity were assessed with the HDAC Fluorescent Activity Assay/Drug Discovery Kit-AK-500 (BIOMOL Research Laboratories) using a FLUOR DE LYSTM that contains an acetylated lysine side chain as a substrate and immunoprecipitated HDAC9-FLAG and HDAC9a-FLAG
25 polypeptides according to the manufacturer's instruction and a SPECTRAMax[®] GEMINI XS microplate spectrofluorometer using the SOFTmax[®] PRO system (Molecular Devices) at excitation 355 nm and emission 460 nm with a cut off filter of 455 nm. Briefly, HDAC9-FLAG and HDAC9a-FLAG were incubated with the substrate overnight at room temperature in a 96-well plate. The reaction was
30 stopped by addition of Fluor De LysTM Developer and samples were read with the fluorometer.

As shown in FIG. 7, both HDAC9-FLAG and HDAC9a-FLAG deacetylated the acetylated lysine of FLUOR DE LYSTM and the activity of HDAC9 and HDAC9a was comparable. To examine the activity of HDAC9 and HDAC9a, inhibition studies using TSA were carried out by preincubating HDAC9-FLAG and HDAC9a-FLAG with TSA for 15 minutes at room temperature. The assay was then carried out as stated above. As shown in FIG. 7, TSA inhibited HDAC9 and HDAC9a deacetylase activity. The inset gel in FIG. 7 shows the amount of protein used in the assay. SAHA, a potent HDAC inhibitor (Richon *et al.*, Proc. Natl. Acad. Sci. USA, 95:3003-3007 (1998)) also completely inhibited the histone deacetylase activity of HDAC9-FLAG and HDAC9a-FLAG. The HDAC activity of HDAC9 and HDAC9a was about ten times lower than the deacetylase activity of HDAC4 when comparable amount of protein was used under conditions tested here.

HDAC9 and HDAC9a enzymatic activity was also determined through HDAC enzymatic assays using ³H-histones isolated from murine erythroleukemia cells as a substrate. This assay was performed essentially as described by Richon *et al.* (Proc. Natl. Acad. Sci. USA, 95:3003-3007 (1998)). Briefly, HDAC9-FLAG and HDAC9a-FLAG were incubated with ³H-histones overnight at 37°C. The reaction was stopped by the addition of 1M HCl/0.1 acetic acid. Released ³H-acetic acid was extracted with ethyl acetate and quantified by scintillation counting. For inhibition studies, the immunoprecipitated complexes were preincubated with the different HDAC inhibitors for 30 minutes at 4°C.

As shown in FIG. 8, HDAC9a-FLAG deacetylated ³H-acetyl-histones. SAHA, a potent HDAC inhibitor also completely inhibited the histone deacetylase activity of HDAC9a-FLAG. TSA also inhibited HDAC9a deacetylase activity. Similar results were obtained when HDAC9 was used as the enzyme source.

HDAC9 and HDAC9a repress MEF2-mediated transcription

The *Xenopus* homolog of HDRP, MITR, was identified as a MEF2 interacting transcriptional repressor (Sparrow *et al.*, EMBO J. 18:5085-5098(1999)) and mouse HDRP also interacts with and represses MEF2 mediated transcription (Zhang *et al.*, J. Biol. Chem. 276:35-39 (2001)). We first tested whether HDAC9-FLAG and HDAC9a-FLAG interact with MEF2. 293 cells were transfected with

vector, HDAC9-FLAG, or HDAC9a-FLAG. The cells were subsequently lysed and HDAC9-FLAG and HDAC9a-FLAG proteins were immunoprecipitated with anti-FLAG antibodies. Western blot analysis of the immunoprecipitated proteins was carried out, using anti-MEF-2 antibody to probe the blot. As shown in FIG. 9A, both HDAC9 and HDAC9a interacted with MEF2 in 293T cells.

It was then determined whether HDAC9 and HDAC9a repress MEF2-mediated transcription. This determination was carried out as follows. The p3XMEF2-luciferase reporter gene (100 ng) and the vector pRL-TK (Promega) (5 ng) were co-transfected into 293T cells in the absence (pcDNA3 empty vector) or presence of MEF2C (100 ng of pCMV-MEF2C). HDAC9-F (1 ng, 10 ng, or 100 ng of pFLAG-HDAC9; pFLAG-HDAC9 and HDAC9-FLAG are different constructs, with the FLAG sequence located at opposite ends of the HDAC9 nucleotide, but are functionally equivalent) or HDAC9a-F (1 ng, 10 ng, or 100 ng of pFLAG-HDAC9a; pFLAG-HDAC9a and HDAC9a-FLAG are different constructs, with the FLAG sequence located at opposite ends of the HDAC9a nucleotide, but are functionally equivalent) was included in a subset of experimental groups with the MEF2C vector. pFLAG empty vector was used to adjust the DNA to an equal amount in each transfection. The cells were harvested 24 to 36 hours after transfection and the luciferase activities were measured using the Dual-Luciferase™ Reporter Assay System from Promega according to the manufacturer's instruction. The firefly luciferase activity was first normalized to the co-transfected Renilla luciferase activity (encoded by the pRL-TK vector), and the luciferase activity value for cells transfected with MEF2C alone was set at 1. MEF2C activated transcription over 30 times the basal level of transcription. As shown in FIG. 9B, HDAC9-FLAG and HDAC9a-FLAG repressed MEF2C mediated transcriptional activation in a dose-dependent manner and completely abolished the activation at the 100 ng dose for both HDAC9 and HDAC9a. The transcriptional repression effect of HDAC9 and HDAC9a on MEF2C mediated transcription was a specific effect since a co-transfected reporter gene for transfection efficiency containing a TK promoter was not repressed by HDAC9 or HDAC9a.

Described herein is the identification and characterization of a new class II HDAC, designated HDAC9. HDAC9 has several alternatively spliced isoforms,

one of which is the previously identified HDRP (Zhou *et al.*, Proc. Natl. Acad. Sci. USA 97:1056-1061 (2000)). HDAC9 and HDAC9a possess HDAC activity, which appears to have a lower specific enzymatic activity than HDAC4. While not wishing to be bound by any particular theory, it is possible that an essential co-factor
5 is lost during immunoprecipitation or does not exist in 293T cells (for example, metastasis-associated protein 2 is essential for the assembly of a catalytically active HDAC1 (Zhang *et al.*, Genes Dev. 13:1924-1935 (1999)), the substrates used are not its natural substrate, or the FLAG tag which interferes with the folding of the protein.

10 Searching the human genome with the HDAC domain from either HDAC1 or HDAC9 identified a total of 10 HDACs in the presently completed human genome sequence, a number of which are schematically represented in FIG. 10. HDACs 1, 2, 3, 8, 4, 5, 6, 7, 9, and 9a all have HDAC domains. HDRP, which is also schematically depicted in FIG. 10, does not have a catalytic domain.

15 All references described herein are incorporated by reference in their entirety. While this invention has been particularly shown and described with reference to preferred embodiment thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the spirit and scope of the invention as defined by the appended
20 claims.

CLAIMS

What is claimed is:

- 5
1. An isolated or recombinant histone deacetylase polypeptide, said polypeptide selected from:
- 10
- a) an isolated or recombinant polypeptide comprising SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10; and
- b) an isolated or recombinant polypeptide having at least 60% sequence identity with any one of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10.
- 15
2. The isolated or recombinant histone deacetylase polypeptide of Claim 1, said polypeptide selected from:
- a) a polypeptide consisting of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10.
- 20
3. The isolated or recombinant histone deacetylase polypeptide of Claim 1, wherein said polypeptide is human.
4. An isolated nucleic acid molecule selected from the group:
- 25
- a) an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9;
- b) a complement of an isolated nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, or SEQ ID NO: 9
- 30
- c) an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10;

- d) a complement of an isolated nucleic acid encoding a histone deacetylase polypeptide of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, or SEQ ID NO: 10;
- e) a nucleic acid that is hybridizable under high stringency conditions to a nucleic acid molecule that encodes any of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, or SEQ ID NO: 8, or a complement thereof; or
- f) a nucleic acid molecule that is hybridizable under high stringency conditions to a nucleic acid comprising SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, or SEQ ID NO: 7; and
- g) an isolated nucleic acid molecule that has at least 55% sequence identity with any one of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 9, or a complement thereof.
5. The isolated nucleic acid molecule of Claim 4, said nucleic acid molecule consisting of the nucleic acid molecule selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, and SEQ ID NO: 9.
6. The isolated nucleic acid molecule of Claim 4, wherein said nucleic acid molecule is human.
7. A vector comprising the isolated nucleic acid molecule of Claim 4.
8. A cell comprising the vector of Claim 7.
9. A cell comprising the isolated nucleic acid molecule of Claim 4.
10. A purified antibody that selectively binds a polypeptide of Claim 1.
11. A method of identifying a compound that modulates expression of a nucleic acid molecule of Claim 4, said method comprising the steps of:

- a) contacting said nucleic acid molecule with a candidate compound under conditions suitable for expression; and
- b) assessing the level of expression of said nucleic acid molecule, wherein a candidate compound that increases or decreases expression of said nucleic acid molecule relative to a control is a compound that modulates expression of said nucleic acid molecule.
- 5
12. The method of Claim 11, wherein said method is carried out in a cell or animal.
- 10
13. The method of Claim 11, wherein said method is carried out in a cell free system.
14. A method of identifying a compound that modulates the enzymatic activity of the polypeptide of Claim 1, said method comprising the steps of:
- 15
- a) contacting said polypeptide with a candidate compound under conditions suitable for enzymatic reaction; and
- b) assessing the enzymatic activity level of said polypeptide, wherein a candidate compound that increases or decreases the enzymatic activity level of said polypeptide relative to a control is a compound that modulates the enzymatic activity of said polypeptide.
- 20
15. The method of Claim 14, wherein said method is carried out in a cell or animal.
- 25
16. The method of Claim 14, wherein said method is carried out in a cell free system.
17. The method of Claim 14, wherein said polypeptide is further contacted with a substrate for the polypeptide, and wherein said substrate is selected from the group consisting of a cell proliferation disease binding agent, an
- 30

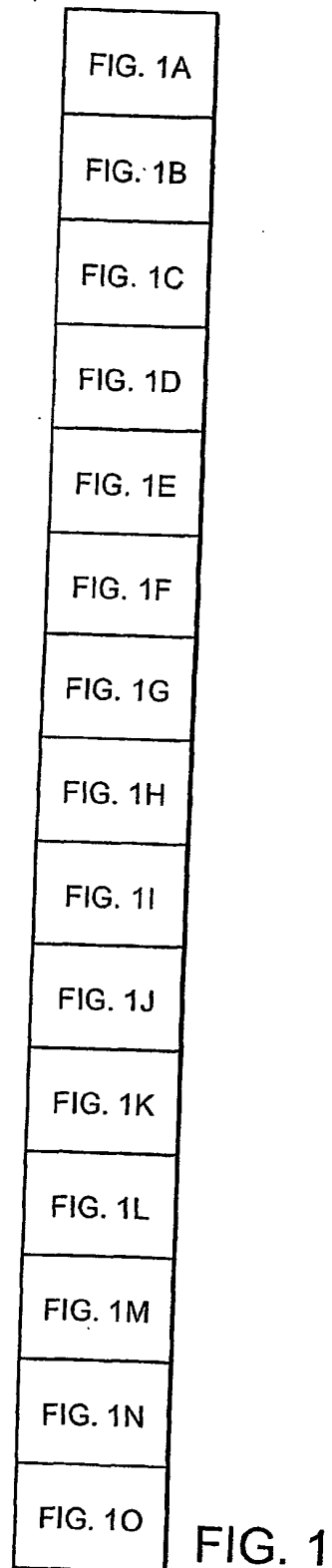
apoptotic disease binding agent, and a cell differentiation disease binding agent.

- 5
18. The method of Claim 17, wherein said candidate compound is an inhibitor.
19. The method of Claim 17, wherein said candidate compound is an activator.
20. A method of identifying a compound that modulates the transcriptional repression activity of the polypeptide of Claim 1, said method comprising
- 10 the steps of:
- a) contacting said polypeptide with a candidate compound under conditions suitable for a transcriptional repression reaction; and
 - b) assessing the transcriptional repression activity level of said polypeptide,
- 15 wherein a candidate compound that increases or decreases the transcriptional repression activity level of said polypeptide relative to a control is a compound that modulates the transcriptional repression activity of said polypeptide.
- 20 21. The method of Claim 20, wherein said method is carried out in a cell or animal.
22. The method of Claim 20, wherein said method is carried out in a cell free system.
- 25
23. The method of Claim 20, wherein said polypeptide is further contacted with a substrate for the polypeptide, and wherein said substrate is selected from the group consisting of a cell proliferation disease binding agent, an apoptotic disease binding agent, and a cell differentiation disease binding
- 30 agent.
24. The method of Claim 23, wherein said candidate compound is an inhibitor.

25. The method of Claim 23, wherein said candidate compound is an activator.
26. A method of identifying a compound that modulates expression of a nucleic acid molecule of Claim 4, said method comprising the steps of:
- 5 a) providing a nucleic acid molecule comprising a promoter region of said nucleic acid of Claim 4 or part of a promoter region of said nucleic acid of Claim 4 operably linked to a reporter gene;
- b) contacting said nucleic acid molecule or with a candidate compound; and
- 10 c) assessing the level of said reporter gene,
- wherein a candidate compound that increases or decreases expression of said reporter gene relative to a control is a compound that modulates expression of said nucleic acid molecule of Claim 4.
- 15 27. The method of Claim 26, wherein said method is carried out in a cell.
28. A method of identifying a polypeptide that interacts with a polypeptide of Claim 1 in a yeast two-hybrid system, said method comprising the steps of:
- 20 a) providing a first nucleic acid vector comprising a nucleic acid molecule encoding a DNA binding domain and said polypeptide of Claim 1;
- b) providing a second nucleic acid vector comprising a nucleic acid encoding a transcription activation domain and a nucleic acid encoding a test polypeptide;
- 25 c) contacting said first nucleic acid vector with said second nucleic acid vector in a yeast two-hybrid system; and
- d) assessing transcriptional activation in said yeast two-hybrid system, wherein an increase in transcriptional activation relative to a control indicates that the test polypeptide is a polypeptide that interacts with said
- 30 polypeptide of Claim 1.
29. A pharmaceutical composition comprising a polypeptide of Claim 1.

30. A method of diagnosing a cell proliferation disease, an apoptotic disease, or a cell differentiation disease in a subject, said method comprising the steps of:
- 5 a) obtaining a sample from said subject; and
- b) assessing the level of activity or expression of said polypeptide of Claim 1 in said sample, or detecting the level of said nucleic acid molecule of Claim 4,
- 10 wherein if said level is increased relative to a control, then said subject has an increased likelihood of having a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, and wherein if said level is decreased relative to a control, then said subject has a decreased likelihood of having a cell proliferation disease, an apoptotic disease, or a cell differentiation disease.
- 15 31. The method of Claim 30, wherein said level of activity or expression of said polypeptide of Claim 1 in said sample is measured using immunohistochemical techniques.
- 20 32. The method of Claim 30, wherein said level of said nucleic acid molecule of Claim 4 in said sample is measured using *in situ* hybridization techniques.
- 25 33. A method of treating a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, said method comprising administering a compound identified by the method of Claim 14.
- 30 34. A method of treating a cell proliferation disease, an apoptotic disease, or a cell differentiation disease, said method comprising administering a compound identified by the method of Claim 20.

'1/173



HDAC93186 bp Coding 151-3186

Exon 1

1 ggggaagaga ggcacagaca cagataggag aagggcaccg gctggagcca cttgcaggac tgagggtttt tgacaacaaa ccctagcagc ctgaagaact
 101 ctaagccaga tgggtggct ggaagagagc agctcttggc tcagcaaaaga atgcacagta tgatcagctc agtggatgtg aagtcagaag ttctctgtggg
 201 cctggagccc atctcaccct tagacctaaG gacagaccctc aggatgatga tggccgtggt ggacctgtt gtccctgaga agcaattgca gcaggaatta
 301 cttcttatcc agcagcagca acaatccag aagcagcttc tgatagcaga gtttcagaaa cagcatgaga acttcacag gcagaccag gctcagcttc
 401 aggagcatat caaggaaCTT ctagccataa AACAGCAACA AGAACTCCTA GAAAGGAGC AGAACTGGA GCAGCAGAGG CAAGAACAGG AAGTAGAGAG
 501 GCATCGCAGA GAACAGCAGC TTCCTCCTCT CAGAGGCCAA GATAGAGGAC GAGAAAGGC AGTGGCACT ACAGAAGTAA AGCAGAAGCT TCAAGAGTTC
 601 CTACTGAGTA AATCAGCAAC GAAAGACACT CCAACTAATG GAAAAATCA TTCCGTGAGC CGCCATCCCA AGCTCTGGTA CACGGCTGCC CACCACACAT
 701 CATTGGATCA AAGCTCTCCA CCCCTTAGTG GAACATCTCC ATCCTACAAG TACACATTAC CAGGAGCACA AGATGCAAG GATGATTCC CCCTTCGAAA
 801 AACTGCCCTCT GAGCCCAACT TGAAGGTGG GTCCAGGTTA AAACAGAAAG TGGCAGAGAG GAGAAGCAGC CCCTTACTCA GCGCGAAGGA TGGAAATGTT

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FIG. 1A

8
 901 GTCACCTTCAT TCAAGAAGCG AATGTTTGAG GTGACAGAAT CCTCAGTCAG TAGCAGTTCT CCAGGCTCTG GTCCAGTTC ACCAAACAAT GGGCCAACCTG
 9
 1001 GAAGTGTAC TGAATAATGAG ACTTGGGTTT TGCCCCCTTAC CCTTCATGCC GAGCAAAATGG TTTTCACAGCA ACGCATTCTA ATTATGAAG ATTCCATGAA
 11
 1101 CCTGCTAAGT CTTTATACCT CTCCTTCTTT GCCCAACATT ACCTTGGGGC TTCCCGCAGT GCCATCCCAG CTCATATGCTT CGAATTCAT CAAAGAAAAG
 12
 1201 CAGAAGTGTG AGAGCAGAC GCTTAGGCAA GGTGTTCTC TGCTGGGCA GTATGAGGC AGCATCCCG CATCTTCCAG CCACCTCAT GTTACTTTAG
 10
 1301 AGGAAAGCC ACCCAACAGC AGCCACCAGG CTCCTCTGCA GCATTTATTA TTGAAAGAAC AAATGCGACA GCAAAGCTT CTTGTAGCTG GTGGAGTTCC
 11
 1401 CTTACATCCT CAGTCTCCT TGGCAACAAA AGAGAGAATT TCACCTGGCA TTAGAGGTAC CCACAAATTG CCCCCTCACA GACCCCTGAA CCGAACCCAGG
 12
 1501 TCTGCACCTT TGCCTCAGAG CACGTTGGCT CAGCTGGTCA TTCAACAGCA ACACCAGCAA TTCTTGGAGA AGCAGAAGCA ATACCAGCAG CAGATCCACA
 1601 TGAACAACT GCTTTGAAA TCTATTGAAC AACTGAAGCA ACCAGGCAGT CACCTTGAGG AAGCAGAGGA AGAGTTCAG GGGGACCAGG CGATGCAGGA
 1701 AGACAGAGCG CCTCTAGTG GCAACAGCAC TAGGAGCGAC AGCAGTCTT GTGTGGATGA CACACTGGGA CAAGTTGGG CTTGTAAGGT CAAGGAGGAA
 1801 CCAGTGGACA GTGATGAAGA TGCTCAGATC CAGGAAATGG AATCTGGGA GCAGGTGCT TTTATGCAAC AGCTTTCCT GGAACCCAG CACACACGTG

FIG. 1B

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1901 CGCTCTCTGT GCGCCAAGCT CCGCTGGCTG CGGTGGCAT GGAIGGATTA GAGAAACACC GTCTGCTC CAGGACTCAC TCTTCCCCTG CTGCCCTCTGT
2001 TTACTCTAC CCAGCAATGG ACCGCCCCCT CCAGCCTGGC TCTGCAACTG GAATIGCCTA TGACCCCTTG ATGCTGAAC ACCAGTGGT TTGTGGCAAT
2101 TCCACCACC ACCCTGAGCA TGCTGGAGA ATACAGAGTA TCTGTTCAG ACTGCAAGAA ACTGGGTGC TAAATAATG TGAGCGAAT CAAGTTCGAA
2201 AAGCCAGCCT GGAGGAATA CAGCTTCTTC ATTCTGAACA TCACTCACTG TTGTATGGCA CCAACCCCTT GGACGGACAG AAGCTGGACC CCAGGATACT
2301 CCTAGGTGAT GACTCTCAA AGTTTTTTC CTCATTACCT TGTGGTGGAC TTGGGGTGA CAGTGACACC ATTTGGAATG AGCTACACTC GTCCGGTGCT
2401 GCACGCATGG CTGTTGGCTG TGTATCGAG CTGGCTTCCA AAGTGGCTC AGGAGAGCTG AAGAAATGGT TTGCTGTGT GAGGCCCTT GGCCATCAG
2501 CTGAAGATC CACAGCCATG GGGTCTGCT TTTTAAATC AGTTGCAAT ACCGCCAAT ACTTGAGAGA CCAACTAAAT ATAAGCAAGA TATGTATTGT
2601 AGATCTGGAT GTTCACCATG GAAAGGTAC CCAGCAGGCC TTTTATGCTG ACCCAGCAT CCTGTACATT TCACTCCATC GCTATGATGA AGGAACTTT
2701 TTCCCTGGCA GTGGACCCC AATGAGGTT GGAACAGGCC TTGGAGAAGG GTACAATATA AATATTGCCT GGACAGGTGG CCTGTATCCT CCCATGGGAG
2801 ATGTTGAGTA CCTTGAAGCA TTCAGGACCA TCGTGAAGCC TGTGGCCAAA GAGTTTGATC CAGACATGGT CTTAGTATCT GCTGGATTG ATGCATTGGA
2901 AGGCCACACC CCTCCTCTAG GAGGTACAA AGTGACGGCA AATGTTTTG GTCAATTGAC GAACAATTG ATGACATTGG CTGATGGACG TGTGGTGTG
3001 GCTCTAGAAG GAGACATGA TCTCAGACC ATCTGTGATG CATCAGAGC CTGTGTAAT GCCTTCTAG GAAATGAGCT GGAGCCACTT GCAGAAGATA
3101 TTCTCCACCA AAGCCCGAAT ATGAATGCTG TTATTTCTTT ACAGAAGATC ATTGAAATTC AAGTATGTC TTAAAGTTC TCTTAA

FIG. 1C

HDAC9a 3499 bp (Coding 151-2790)

Exon 1

1 ggggaaagaga ggcacagaca cagataggag aagggcaccg gctggagcca cttgcaggac tgagggtttt tgcaacaaaa ccctagcagc ctgaagaact

101 ctaagccaga tggggtggct ggacgagagc agctcttggc tcagcaaaaga atgcacagta tgatcagctc agtggatgtg aagtcagaag ttctctgtggg

201 cctggagccc atctcactt tagaccttaag gacagacctc aggatgatga tgccccgtggt ggaccctggt gtccgtgaga agcaattgca gcaggaatta

301 cttcttatcc agcagcagca acaaattccag aagcagcttc tgatagcaga gtttcagaaa cagcatgaga acttgacacg gcagcaccag gctcagcttc

401 aggagcatat cagggaactt ctagccataa aacagcaaca agaactccta gaaaagcagc agaaactgga gcagcagagg caagaacagg aagtagagag

501 gcatgcaga gaacagcagc ttctctctct cagaggcaaa gatagaggac gagaaaggc agtggcaagt acagaagtaa agcagaagct tcaagagttc

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FIG. 1D

5
601 C T A C T G A G T A A A T C A G C A C G A A G A G A C A C T C C A A C T A A T G G A A A A A T C A T T C C G T G A G C G C C A T C C C A A G C T C T G G T A C A G G G T G C C C A C C A C A C A T
6
701 C A T T G G A T C A A A G C T C T C C A C C C T T A G T G A A C A T C T C C A T C T A A G T A C A C A T T A C C A G G A C A C A G A T G C A A A G G A T G A T T T C C C C T T C G A A A
7
801 A A C T G C C T C T G A G C C C A C T T G A A G G T G C G G T C C A G G T T A A A C A G A A A G T G G C A G A G A G G A G A G A G C A G C C C T T A C T C A G G C G A A G G A T G G A A A T G T T
8
901 G T C A C T T C A T T C A A G A A G C G A A T G T T T G A G G T C A G A A T C C T C A G T C A G T A G C A G T T C T C C A G G C T C G T C C C A G T T C A C C A A C A A T G G G C C A A C T G
9
1001 G A A G T G T T A C T G A A A A T G A G A C T T C G G T T T G C C C C C T A C C C T C A T G C C G A G C A A A T G G T T T C A C A G C A A C G C A T T C T A A T T C A T G A A A T T C C A T G A A
10
1101 C C T G C T A A G T C T T T A T A C C T C T C C T T C T T T G C C C A A C A T T A C C T T G G G C T T C C G C A G T G C C A T C C C A G C T C A A T G C T T C G A A T T C A C T C A A G A A A A G
11
1201 C A G A A G T G T G A G C G C A G A C G C T T A G G C A A G G T G T T C C T C T G C A G T A T G G A G C G T A T G G A G G C A G C A T C C G G C A T C T T C C A G C C A C C T C A T G T T A C T T T A G
1301 A G G G A A A G C C A C C C A A C A G C A G C C A C C A G G C T C T C C T G C A G C A T T A T T A T T G A A A G A A C A A A T G C A C A A A A G C T T C T T G A G C T G T G G A G T T C C
1401 C T T A C A T C C T C A G T C T C C C T T G G C A A C A A A A G A G A G A A T T T C A C C T G G C A T T A G A G T A C C C A A A A T T G C C C C T C A C A G A C C C C T G A A C C G A A C C C A G
1501 T C T G C A C C T T T G C C T C A G A C A C G T T G G C T C A G T T G G C T T T C A C A G C A A C A C C A G C A A T T C T T G G A G A G C A A G C A A T T A C C A G C A G C A G A T C C C A

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FIG. 1E

1601 TGAACAACT GCTTTCGAAA TCTANTGAAC AACTGAAGCA ACCAGGCAGT CACCTTGAGG AAGCAGAGGA AGAGTTTCAG GGGGACCAGG CGATGCAGGA
12
1701 AGACAGAGCG CCTCTAGTG GCAACAGCAC TAGGAGCGAC AGCAGTGCTT GTGTGGATGA CACACTGGGA CAAGTTGGGG CTGTGAAGGT CAAGGAGGAA
1801 CCAGTGGACA GTGATGAAGA TGCTCAGATC CAGGAATAGG AATCTGGGGA GCAGGCTGCT TTTATGCAAC AGCCTTTCCT GGAACCCACG CACACACGTG
14
1901 CGCTCTCTGT GCGCCAAGCT CCGCTGGCTG CCGTTGGCAT GGATGGATTA GAGAAACACC GTCTGCTCTC CAGGACTCAC TCTTCCCCCTG CTGCCTCTGT
2001 TTFACTCAC CCAGCAATGG ACCGCCCCCT CCAGCCTGGC TCTGCAACTG GAATTCCTTA TGACCCCTTG ATGCTGAAAC ACCAGTGCCT TTGTGGCAAT
15
2101 TCCACCACC ACCCTGAGCA TGCTGGAGCA ATACAGAGTA TCTGTCAAG ACITGAGAA ACTGGGCTGC TAAATAATG TGAGCGAAT CAAGTTCGAA
16
2201 AAGCCAGCCT GGAGGAATA CAGCTTGTC ATTCTGAACA TCCTCACTG TTGTATGGCA CCAACCCCT GGACGGACAG AAGCTGGACC CCAGGATACT
17
2301 CCTAGTGAT GACTCTCAA AGTTTTTTC CTCATTACCT TGTGGTGGAC TTGGGTGGA CAGTGACACC ATTTGGAATG AGCTACACTC GTCCGGTGCT
18
2401 GCACGCATGG CTGTTGGCTG TGTATGAG CTGGCTTCCA AAGTGGCCTC AGGAGAGCTG AAGAATGGGT TTGCTGTGT GAGGCCCT GGCCATCAGG
19
2501 CTGAAGAATC CACAGCCATG GGGTCTCTGT TTTTAAATC AGTTGCAAT ACCGCCAAT ACTTGAGAGA CCACTAAT ATAAGCAAGA TATTGATTGT
20

FIG. 1F

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21
2601 TACATCTGGAT GTTCACCATG GAAACGGTAC CCACGAGGC TTTTAGCTG ACCCAGCAT CCCTACATT TCACTCCATC GCTAUGATGA AGGGAACCTT
2701 TTCCCTGGCA GTGAGCCCC AATGAGGTT CGGTTTATTT CTTAGAGCC CCACTTTTAT TTGTATCTTT CAGGTAATG CATTGCATGA ttacccttaa
STOP CODON
22
2801 ttttcttctc ctttgttgtt gttttaatt acacgagatt atbgaattgt cccatgggac caagaaccag tgcagaacaa gtgcataacc cagagcactg
2901 tttgtcaggg aaggttgggc tgatttgatg tgttgtttga tgtttatttc aagagctccc atgtgcttgt tttcctctct tcttgcttcc ttccatttgc
3001 tctcttctct gcccaaccgt gtgtgtcttt ctcttcccag gttagaacag gccttgaga aggtacaat ataaatattg cctggacagg tggccttgat
3101 cctcccattg gagatgttga gtaccttgaa gcattcagga ccactgtgaa gcctgtggcc aaagagtttg atccagacat ggtcttagta tctgctggat
3201 ttgatgcatt ggaaggccac accctcctc taggagggtg caaagtgcg gcaaaatggt ttggtcattt gacgaagcaa ttgatgacat tggctgatgg
3301 acgtgttgtg ttggctctag aaggaggaca tgatctcaca gccatctgtg atgcacaga agcctgtgta aatgcccttc taggaaatga gctggagcca
3401 ctgcagaag atattctcca ccaagcccg aatatgaatg ctgttatttc ttacagaag atcattgaaa ttcaaagat gtctttaag ttctcttaa

FIG. 1G

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>HDRP (deltaNLS)

```

1  ggggaagaga ggcacagaca cagataggag aagggcaccc gctggagcca
51  ctgacaggac tgagggtttt tgacaacaaa ccctagcagc ctgaagaact
101  ctaagccaga tgggttggtt ggacgagagc agctcttggc tcagcaaaaga
151  atgcacagta tgatcagctc atctcacctt tagacctaat gacagacctc aggatgatga
201  cctggagccc tgccccgtgt ggacctgtt gtccgtgaga agcaattgca gcaggaatta
251  tgccccgtgt ggacctgtt gacacctaat acaaatccag aagcagcttc tgatagcaga
301  cttcttatcc agcagcagca acttgacacg gcagcaccag gctcagcttc
351  gtttcagaaa cagcatgaga acttgacacg gcagcaccag gctcagcttc
401  aggagcatat caaggaaact gcagcagagg ttcctcctct cagaggcaaa gatagaggac
451  gaaaaggagc agaaactgga gaagcagagg caagaacagg aagtagagag
501  gcacgcgaga gaacagcagc ttcctcctct cagaggcaaa gatagaggac
551  gagaaagggc agtggcaagt acagaagtaa agcagaagct tcaagagattc
601  ctactgagta aatcagcaac gaaagacact ccaactaatg gaaaaaatca
651  ttccgtgagc cgccatccca agctctggta cagggtgccc caccacacat
701  cattggatca aagctctcca agctctggta cagggtgccc caccacacat
751  tacacattac caggagcaca agctctggta cagggtgccc caccacacat
801  aactgaatcc tcagtcagta gcagttctcc aggtcttggc cccagttcac
851  caaacaatgg gccaactgga agtgttactg aaaaatgagac ttcgggtttg
901  ccccctaccc ctcatgccga gcaaatggtt tcacagcaac gcatttctaat
951  tcatgaagat tccatgaacc tgctaagtct ttatacctct ccttctttgc
1001 ccaacattac cttggggctt cccgcagtgc catcccagct caatgcttgc

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FIG. 1H

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1051 aattcactca aagaaaagca gaagtgtgag acgcagacgc ttaggcaagg
1101 tgttcctctg cctgggcagt atggaggcag catcccgga tcttccagcc
1151 accctcatgt tacttttagg gaaagccac ccaacagcag ccaccaggct
1201 ctcctgcagc atttattatt gaaagaacaa atgcgacagc aaaagcttct
1251 tgtagctggt ggagttccct tacatcctca gtctcccttg gcaacaaaag
1301 agagaatttc acctggcatt agaggtaccc acaaattgcc ccgtcacaga
1351 cccctgaacc gaaccagtc tgcacctttg cctcagagca cgttgggtca
1401 gctggtcatt caacagcaac accagcaatt cttggagaag cagaagcaat
1451 accagcagca gatccacatg aacaaactgc ttctgaaatc tattgaacaa
1501 ctgaagcaac caggcagtca ccttgaggaa gcagagggaag agcttcaggg
1551 ggaccaggcg atgcaggaag acagagcgcc ctctagtggc aacagcacta
1601 ggagcgacag cagtgttgt gtggatgaca cactgggaca agtggggct
1651 gtgaagggtca aggaggaacc agtggacagt gatgaagatg ctcagatcca
1701 ggaatggaa tctggggagc aggtgtcttt tatgcaacag gtaataggca
1751 aagatttagc tccaggattt gtaattaaag tcattatctg a
```

FIG. 11

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>HDAC9 (deltaNLS)

```

1  ggggaagaga  ggcacagaca  cagataggag  aaggcaccg  gctggagcca
51  cttgcaggac  tgagggtttt  tgcaacaaaa  ccctagcagc  ctgaagaact
101  ctaagccaga  tggggtggct  ggacgagagc  agctcttggc  tcagcaaaaga
151  atgcacagta  tgatcagctc  agtggatgtg  aagtcagaag  ttctgtggg
201  cctggagccc  atctcacctt  tagacctaa  gacagacctc  aggatgatga
251  tgcccgtggt  ggaccctggt  gtccgtgaga  agcaattgca  gcaggaatta
301  cttcttatcc  agcagcagca  acaaatccag  aagcagcttc  tgatagcaga
351  gtttcagaaa  cagcatgaga  acttgacacg  gcagcaccag  gctcagcttc
401  aggagcatat  caaggaaactt  ctagccataa  aacagcaaca  agaactccta
451  gaaaaggagc  agaaactgga  gcagcagagg  caagaacagg  aagtagagag
501  gcatacgaga  gaacagcagc  ttctctctct  cagaggcaaa  gatagaggac
551  gagaaagggc  agtggcaagt  acagaagtaa  agcagaagct  tcaagagttc
601  ctactgagta  aatcagcaac  gaaagacact  ccaactaatg  gaaaaaatca
651  ttccgtgagc  cgccatccca  agctctggt  cagggtgcc  caccacacat
701  cattggatca  aagctctcca  ccccttagtg  gaacatctcc  atcctacaag
751  tacacattac  caggagcaca  agatgcaaa  gatgatttc  cccttcgaaa
801  aactgaatcc  tcagtcagta  gcagtctctc  aggctctggt  ccagttcac
851  caaacaatgg  gccaaactga  agtgttactg  aaaatgagac  ttcggttttg
901  cccctaccc  ctcatgccga  gcaaatggtt  tcacagcaac  gcattctaat
951  tcatgaagat  tccatgaacc  tgctaagtct  ttatacctct  ctttctttgc
1001  ccaacattac  cttgggggctt  cccgcagtgc  catcccagct  caatgcttcg
1051  aattcactca  aagaaaagca  gaagtgtgag  acgcagacgc  ttaggcaagg
1101  tgttcctctg  cctgggcagt  atggaggcag  catccggca  tcttcagcc

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FIG. 1J

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1151 accctcatgt tacttttagag ggaaagccac ccaacagcag ccaccaggct-
1201 ctccctgcagc atttattatt gaaagaacaa atgcgacagc aaaagcttct
1251 tgtagctggt ggagttccct tacatcctca gtctcccttg gcaacaaaag
1301 agagaatttc acctggcatt agaggtaccc acaaattgcc ccgtcacaga
1351 cccctgaacc gaaccagtc tgcacctttg cctcagagca cgttggctca
1401 gctggtcatt caacagcaac accagcaatt cttggagaag cagaagcaat
1451 accagcagca gatccacatg aacaaactgc ttctgaaatc tattgaacaa
1501 ctgaagcaac caggcagtca ccttgaggaa gcagaggaa agcttcaggg
1551 ggaccaggcg atgcaggaag acagagcgcc ctctagtggc aacagcacta
1601 ggagcgacag cagtgcctgt gtggatgaca cactgggaca agttggggct
1651 gtgaagggtca aggaggaacc agtggacagt gatgaagatg ctcatatcca
1701 ggaaatggaa tctggggagc aggtgccttt tatgcaacag cctttccctgg
1751 aaccacagca cacacgtgcg ctctctgtgc gccaaagctcc gctggctgcg
1801 gttggcatgg atggattaga gaaacacgtt ctcgctctca ggactcactc
1851 ttcccctgct gcctctgttt tacctcacc ccgaatggac cgccccctcc
1901 agcctggctc tgcaactgga attgcctatg accccttgat gctgaaacac
1951 cagtgcgttt gtggcaattc caccacccac cctgagcatg ctggacgaat
2001 acagagtatc tggtcacgac tgcaagaaac tgggctgcta aataaatgtg
2051 agcgaattca aggtcgaaaa gccagcctgg aggaaataca gcttgttcat
2101 tctgaacatc actcactgtt gtatggcacc aaccctctgg acggacagaa
2151 gctggacccc aggatactcc tagtgatga ctctcaaaag tttttttcct
2201 cattaccttg tggtagactt ggggtggaca gtgacaccat ttggaatgag
2251 ctacactcgt ccggtgctgc acgcatggct gtggctgtg tcatcgagct
2301 ggcttccaaa gtggcctcag gagagctgaa gaatgggttt gctgttgtga
2351 ggccccctgg ccatacagct gaagaatcca cagccatggg gttctgcttt
2401 tttaattcag ttgcaattac cgccaaatac ttgagagacc aactaaatat

FIG. 1K

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2451 aagcaagata ttgattgtag atctggatgt tcaccatgga aacggtaccc  
2501 agcaggcctt ttatgctgac ccagcatec  tgtacatttc actccatcgc  
2551 tatgatgaag ggaacttttt cctggcagt  ggagcccaa atgaggttgg  
2601 aacaggcctt ggagaagggt acaataaaa  tattgcctgg acaggtggcc  
2651 ttgattcctc catgggagat gttgagtacc ttgaagcatt caggaccatc  
2701 gtgaagcctg tggccaaaga gtttgatcca gacatggtct tagtatctgc  
2751 tggatttgat gcattggaag gccacacccc tcctctagga gggtacaaag  
2801 tgacggcaaa atgttttggg catttgacga agcaattgat gacattggct  
2851 gatggacgtg tgggtgtggc tctagaagga ggacatgata tcacagccat  
2901 ctgtgatgca tcagaagcct gtgtaaatgc ccttctagga aatgagctgg  
2951 agccacttgc agaagatatt ctccaccaaa gccgaatat gaatgctgtt  
3001 atttctttac agaagatcat tgaattcaa  agtatgtctt taaagtcttc  
3051 ttaa
```

FIG. 1L

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>HDAC9a (deltaNLS)

```

1  ggggaagaga  ggcacagaca  cagataggag  aagggcaccg  gctggagcca
51  cttgcaggac  tgagggtttt  tgacaacaaa  ccctagcagc  ctgaagaact
101 ctaagccaga  tgggtgggt  ggacgagagc  agctcttggc  tcagcaaaaga
151 atgcacagta  tgatcagctc  atctcacctt  tagacctaa  agtcagaag  ttctgtggg
201 cctggagccc  atctcacctt  tagacctaa  gacagacctc  aggatgatga
251 tgcccgtggt  ggacctgtt  gtccgtgaga  agcaattgca  gcaggaatta
301 cttcttatcc  agcagcagca  acaaatccag  aagcagcttc  tgatagcaga
351 gtttcagaaa  cagcatgaga  acttgacacg  gcagcaccag  gctcagcttc
401 aggagcatat  caaggaactt  ctaggcataa  aacagcaaca  agaactccta
451 gaaaaggagc  agaaactgga  gcagcagagg  caagaacagg  aagtagagag
501 gcctgcgaga  gaacagcagc  ttctctctct  cagaggcaaa  gatagaggac
551 gagaaagggc  agtggcaagt  acagaagtaa  agcagaagct  tcaagagttc
601 ctactgagta  aatcagcaac  gaaagacact  ccaactaatg  gaaaaaatca
651 ttccgtgagc  cgccatccca  agctctggt  caggctgcc  caccacacat
701 cattggatca  aagctctcca  ccccttagtg  gaacatctcc  atctacaag
751 tacacattac  caggagcaca  agatgcaaa  gatgatttcc  cccttcgaaa
801 aactgaatcc  tcagtcagta  gcagttctcc  aggctctggt  ccagttcac
851 caaacaatgg  gccaaactgga  agtgttactg  aaaatgagac  ttcggttttg
901 cccctaccc  ctcatgccga  gcaaatggtt  tcacagcaac  gcatttctaat
951 tcatgaagat  tccatgaacc  tgctaagtct  ttatacctct  cttctttgc
1001 ccaacattac  ctggtggctt  ccgcagtgc  catcccagct  caatgcttcg
1051 aattcactca  aagaaaagca  gaagtgtgag  acgcagacgc  ttaggcaagg
1101 tgttcctctg  cctgggcagt  atggaggcag  catccggcga  tcttcagcc
1151 accctcatgt  tactttagag  ggaaagccac  ccaacagcag  ccaccaggct

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FIG. 1M

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1201 ctccctgcagc atttattatt gaaagaacaa atgcgacagc aaaagcttct
1251 tgtagctggg tgagttccct tacatcctca gtctcccttg gcaacaaaag
1301 agagaatttc acctggcatt agaggctacc agaatgtcc ccgtaacaga
1351 cccctgaacc gaaccagtc caacagcaac accagcaatt cctcagagca cgttggtca
1401 gctgggtcatt accagcagca gatccacatg acaaaactgc ttgcgaaatc cagaagcaat
1451 accagcagca ctgaagcaac caggcagtca ccttgaggaa gcagaggag agcttcagg
1501 ggaccaggcg atgcaggaag acagagcgcc ctctagtggc aacagcacta
1551 ggagcgacag cagtgccttg gtgatgaca cactgggaca agtggggct
1601 gtgaagggtca aggaggacc agtgacagt gatgaagatg ctcatgcc
1651 ggaatggaa tctggggagc aggtgcttt tatgcaacag cctttcctgg
1701 aaccacgca cacacgtgcg ctctctgtgc gccaaagtcc gctggctgcg
1751 gttggcatgg atggattaga gaaacacgt ctctctcca ggactcactc
1801 tccccctgct gcctctgttt tacctcacc agcaatggac cgccccctcc
1851 agcctggctc tgcaactgga attgcctatg accccttgat gctgaaacac
1901 cagtgcgttt gtggcaattc caccaccac cctgagcatg ctggacgaat
1951 acagagtatc tggtcacgac tgcaagaaac tgggctgcta aataaatgtg
2001 agcgaattca aggtcgaaaa gccagcctgg aggaaataca gcttggtcat
2051 tctgaacatc actcactgtt gtatggcacc aacccccctgg acggacagaa
2101 gctggacccc aggatactcc taggtgatga ctctcaaaag ttttttctc
2151 cattaccttg tggaggactt ggggtggaca gtgacaccat ttggaatgag
2201 ctacactcgt ccggtgctgc acgcatggct gttggctgtg tcatcgagct
2251 ggcttccaaa gtggcctcag gagagctgaa gaatgggttt gctgttgtga
2301 ggccccctgg ccatcacgt gaagaatcca cagccatggg gttctgcttt
2351 ttttaattcag ttgcaattac cgccaaatac ttgagagacc aactaaatat
2401

FIG. 1N

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```
2451 aagcaagata ttgattgtag atctggatgt tcaccatgga aacggtaccc
2501 agcaggcctt ttatgctgac ccagcatcc tgtacatttc actccatcgc
2551 tatgatgaag ggaacttttt ccctggcagt ggagcccaa atgaggttcg
2601 gtttatttct ttagagcccc acttttattt gtatctttca ggtaattgca
2651 ttgcatgatt acccctaatt ttcttgcct ttgctggtgt tttaaattac
2701 acgagattac tgaattgtcc catgggacca agaaccagtg cagaacaagt
2751 gcataaacca gagcactgtt tgtcaggga ggctgggctg atttgatgtg
2801 ttgtttgatg ttatttcaa gagctcccat gtgcttggtt tcctctcttc
2851 ttgcttttct ccatttgctc tcttctctgc ccaccgtgt gtgtctttct
2901 cttcccaggt tggaacaggc ctggagaag ggtacaatat aaatattgcc
2951 tggacagggt gccttgatcc tccatggga gatgttgagt accttgaagc
3001 attcaggacc atcgtgaagc ctgtggccaa agagtttgat ccagacatgg
3051 tcttagtata tgctggattt gatgcattgg aaggccacac cctcctcta
3101 ggaggggtaca aagtgcggc aaaatgtttt ggtcatttga cgaagcaatt
3151 gatgacattg gctgatggac gtgtggtgtt ggctctagaa ggaggacatg
3201 atctcacagc catctgtgat gcatcagaag cctgtgtaaa tgcccttcta
3251 ggaatgagc tggagccact tgcagaagat attctccacc aaagcccgaa
3301 tatgaatgct gttatttctt tacagaagat cattgaaatt caaagtatgt
3351 ctttaaagtt ctcttaa
```

FIG. 10

FIG. 2A
FIG. 2B
FIG. 2C
FIG. 2D
FIG. 2E

>HDAC9 (1011 amino acids)
 MHSMISSVDVKSEVPVGLPI SPLDLRLTDLRMMPVDPVVRKQLQQELLIIQQQQQI
 QKQLLIAEFQKHENLTRQHQALQEHIKELLAIKQQQELLEKEQKLEQQRQEVEVERH
 RREQQLPPLRGKDRGRERAVASTEVKQLQEFLLSKSATKDTPTNGKNHSVSRHPKLMY
 TAAHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDDFPLRKTASEP NLKVR SRLKQKVAE
 RRSPLLRKDG NVVTSFKKRMFEVTESSVSSSPGSGPSPNNGPTGSVTENETSVLP
 PTPHAEQMV SQORILIHEDSMNLLSLYTSPSLPNI TLGLPAVPSQLNASNSLKEKQKCE
 TQTLRQGVPLPGQYGGSI PASSSHPHVTLEGKPPNSSHQALLQHLLLKEQMRQKLLVA
 GGVPLHPQSPLATKERISPGIRGTHKLPRHRPLNRTQSAPIPOSTLAQLVIQQQHQQFL
 EKQKQYQQQIHMNKL LSKSIEQLKQPGSHLEEAEEEEELQGDQAMQEDRAPSSGNSTRSDS
 SACVDDTLGQVGAVKVEEPVDSDEDAQIQEMESGEQA AFMQQPFLEPTHTRALSVRQA
 PLAAVGM DGLEKHRLVSRTHSSPAA SVLPHPAMDRPLQPGSATGIAYDPLMLKHQCVCG
 NSTTHPEHAGRIQSIWSRLQETGLINKCERIQGRKASLEEIQLVHSEHSLLYGTNPLD
 GQKLDPRILLGDDSQKFFSSLPCGGLGVDSDTIWNELHSSGAARMAVGCVIELASKVAS
 GELKNGFAVVRPPGHHAEEESTAMGFCFFNSVAITAKYLRDQLNISKILIVDL DVHHGNG
 TQQAFYADPSILYISLHRYDEGNFFPGSGAPNEVGTGLGEGYNINIAWTGGLDPPMGDV
 EYLEAFRTIVKPVAKFDPDMVLVSAGFDAL EGTPTPLGGYKVTAKCFGH LTKQLMTLA
 DGRVVLAL EGGHDLTAICDASEACVNALLGNELEPLAEDILHQSPNMNAVISLQKIIEI
 QMSLKF S

FIG. 2A

FIG. 2

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>HDAC9a (879 amino acids)
NHSMISSVDVKSEVPVGLPIPLDLRLTDLRMMPVVDPVVREKQLQQELLIIQQQQQI
QKQLLIAEFQKQHNLTRQHQAOQLQEHKELLAIKQQQELLEKEQKLEQQRQEQEVERH
RREQQLPPLRGKDRGRERAVASTEVKQLQEFFLLSKSATKDTPTNGKNHSVSRHPKLWY
TAAHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDDFPLRKTASEP NLKVRSLKQKVAE
RRSSPLLRRKDG NVVTSFKKRMFEVTESVSSSSPGSGPSSPNNGPTGSVTENETSVLP
PTPHAEQMV SQQRILIHEDSMNLLSLYTSPSLPNI'TLGLPAVPSQLNASNSLKEKQKCE
TQTLRQGVPLPGQYGGSI PASSSHPHVTLEKPPNSSHQALLQHLLLKEQMRQKLLVA
GGVPLHPQSP L ATKERISPGIRGTHKLP RHRPLNRTQSA PLPQSTLAQLV IQQHQQFL
EKQKQYQQQIHMNKLLSKSIEQLKQPGSHLEAEELQGDQAMQEDRAPSSGNSTRSDS
SACVDDTLGQVGAVKVKEEPVDSDEDAQIQEMESGEQA AFMQQPFLEPTHTRALSVRQA
PLAAVGMDGLEKHLVSRTHSSPAA SVLPHPAMDRPLQPGSATGIA YDPLMLKHQCVCG
NSTTHPEHAGRIQSIWSRLQETGLLNKCERIQGRKASLEEIQLVHSEHHSLLYGTNPLD
GQKLDPRILLGDDSQKFFSSLPCGGLGVDSDTIWNELHSSGAARMAVGCVIELASKVAS
GELKNGFAVVRPPGHHAEESTAMGFCFFNSVAITAKYLRDQLNISKILIVDLDVHHGNG
TQQA FYADPSILYISLHRYDEGNFFPGSGAPNEVRFISLEPHFYLYLSGNCIA

FIG. 2B

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>HDAC9 (ANLS) (967 amino acids)
 MHSMISSVDVKSEVPVGLPEISPLDLRTDLRMMMPVDPVREKQLQQELLIIQQQQQI
 QKQLLIAEFQKQHENLTRQHQAQLQEHIKELLAIKQQQELLEKEQKLEQQRQEVEVERH
 RREQQLPPLRGKDRGRERAVASTEVEKQLQEFFLLSKSATKDTPTNGKNHSVSRHPKLMY
 TAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDDFPLRKTESSVSSSPGSGPSSPNN
 GPTGSVTENETSVLPPTPHAEQMVQQRIILIHEDSMNLLSLYTSPLPNIITLGLPAVPS
 QLNASNLSLKEKQKCETQTLRQGVPLPGQYGGSI PASSSHPHVTLEGKPPNSSHQALLQH
 LLLKEQMRQQKLLVAGGVPLHPQSPLATKERISPGIRGTHKLPRHRPLNRTQSAPLPQS
 TLAQLVIQQQHQQFLEKQKQYQQQIHMNKLKLSKIEQLKQPGSHLEAEELQGDQAMQ
 EDRAPSSGNSTRSDSSACVDDTLGQGVAVKKEEPVDSDEDAQIQEMESGEQA AFMQQP
 FLEPTHTRALSVRQAPLAAVGMDGLEKHRLVSRTHSSPAASVLPHPAMDRPLQPGSATG
 IAYDPLMLKHQCVCGNSTTHPEHAGRIQSIWSRLQETGLLNKCERIQGRKASLEEIQLV
 HSEHHSLLYGTNPLDGQKLDPRILLGDDSQKFFSSLPCCGLGVDSDTIWNELHSSGAAR
 MAVGCVIELASKVASGELKNGFAVVRPPGHHAEEESTAMGFCFFNSVAITAKYL RDQLNI
 SKILIVDL DVHHGNGTQQAFYADPSILYISLHRYDEGNFFPGSGAPNEVGTGLGEGYNI
 NIAWTGGLDPPMGDVEYLEAFRTIVKPVAKFDPDMVLVSAGFDALEGHTPPLGGYKVT
 AKCFGHLTKQLMTLADGRVVLALEGHDLTAICDASEACVNALLGNELEPLAEDILHQ
 PNMNNAVISLQKIIIEIQMSLSLKFS

FIG. 2C

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>HDAC9a (ΔNLS) (835 amino acids)
MHSMISSVDVKSEVPVGLPEISPLDLRTDLRMMPVDPVREKQLQQLLLIQQQQI
QKQLLIAEFQKHENLTRQHQALQEHIKELLAIKQQQLLEKEQKLEQQRQEQEVERH
RREQQLPPLRGKDRGRERAVASTEVKQLQEFFLLSKSATKDTPTNGKNHSVSRHPKLWY
TAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDDFPLRKTESSVSSSPGSGPSSPNN
GPTGSVTENETSVLPPTPHAEQMVSQQRILIHEDSMNLLSLYTSPLPNITLGLPAVPS
QLNASNSLKEKQKCEQTQLRQGVPLPGQYGGIPASSSHPHVTLEGKPPNSSHQALLQH
LLLKEQMRQQKLLVAGVPLHPQSPLATKERISPGIRGTHKLPRHRPLNRTQSAPLPQS
TLAQLVIQQHQHFLEKQKQYQQQIHMNKLKSKIEQLKQPGSHLEEAEEELQGDQAMQ
EDRAPSSGNSTRSDSSACVDDTLGQVGAVKVKEEPVDSDEDAQIQEMESGEQAQFMQOP
FLEPHTRALSVRQAFLAAVGMDGLEKHLVSRTHSSPAASVLPHPAMDRPLQPGSATG
IAYDPLMLKHQCVCGNSTTHPEHAGRIQSIWSRLQETGLLNKCEIRIQGRKASLEEIQLV
HSEHSHLLYGTNPLDGGKLDPRILLGDDSQKFFSSSLPCGGLGVDSDTIWNELHSSGAAR
MAVGCVIELASKVASGELKNGFAVVRPPGHAAEESTAMGFCFFNSVAITAKYLRDQLNI
SKILIVDLDVHHGNGTQQAFYADPSILYISLHRYDEGNFFPGSGAPNEVRFISLEPHFY
LYLSGNCIA

FIG. 2D

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>HDRPa (HDRP ΔNLS) (546 amino acids)
MHSMISSVDVKSEVPVGLPEISPDLRLTDLRMMMPVDPVVRKQLQQELLIIQQQQQI
QKQLLIAEFQKQHENTRQHQAQLQEHKELLAIKQQQELLEKEQKLEQQRQEQEVERH
RREQQLPPLRGKDRGRERAVASTEYKQKLQEFLLSKSATKDTPTNGKNHSVSRHPKLWY
TAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDDFPLRKTESSVSSSPGSGPSSPNN
GPTGSVTENETSVLPPTPHAEQMVVSQQORILIHEDSMNLLSLYTSPSLPNI TLGLPAVPS
QLNASNSLKEKQKCEQTQLRQGVPLPGQYGGSI PASSSHPHVTLEKPPNSSHQALLQH
LLLKEQMRQQKLLVAGGVPLHPQSPPLATKERISPGIRGTHKLPRHRPLNRTQSAPLPQS
TLAQLVIQQQHQQFLEKQKQYQQQIHMNKLKSKSIEQLKQPGSHLEEAEEELQGDQAMQ
EDRAPSSGNSTRSDSSACVDDTLGQVGAVKVKEEPVDSDEDAQIQEMESGEQA AFMQQV
IGKDLAPGFVIKVI I

FIG. 2E

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FIG. 3A
FIG. 3B
FIG. 3C

FIG. 3

FIG. 3A

1	HDAC9a	-----	MHSMISSVDVKSEVPVGLPEP	-ISPLDLRTDLRMMMP
1	HDAC9	-----	MHSMISSVDVKSEVPVGLPEP	-ISPLDLRTDLRMMMP
1	HDAC4	-----	MHSMISSVDVKSEVPVGLPEP	-ISPLDLRTDLRMMMP
			MSSQSHPDGLSGRDQPVLLNPAR	VNHMPSTIVDVATIALEPLQVAPSAVEMDLRTDHQFSILP
36	HDAC9a		VVDPVVRKLOOELLII	00000IOKOLLIAEFKOKOHENLTROHOAOLOEHIK
36	HDAC9		VVDPVVRKLOOELLII	00000IOKOLLIAEFKOKOHENLTROHOAOLOEHIK
36	HDAC4		VVDPVVRKLOOELLII	00000IOKOLLIAEFKOKOHENLTROHOAOLOEHIK
61			VAEPALREQQLOOELLIA	LKQKQOIQRQIILIAEFQROHEQLSRQHEAQLHEHIKQQQEMLA
93	HDAC9a		IKOOQELLEKEQKLE	QOORQOEVEVRRRREOOLPPLRGKDRGRERAVASTEVEKOKLOEFFLL
93	HDAC9		IKOOQELLEKEQKLE	QOORQOEVEVRRRREOOLPPLRGKDRGRERAVASTEVEKOKLOEFFLL
93	HDAC4		IKOOQELLEKEQKLE	QOORQOEVEVRRRREOOLPPLRGKDRGRERAVASTEVEKOKLOEFFLL
121			MKHQOELLEHQKLE	HRHQERHROEQEELKQHQREQKLOQLKNEKQKESAVASTEVEKMKLOEFFVL
153	HDAC9a		SKSATKDTPTNGKNHVS	SRHPKLMWYTAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDD
153	HDAC9		SKSATKDTPTNGKNHVS	SRHPKLMWYTAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDD
153	HDAC4		SKSATKDTPTNGKNHVS	SRHPKLMWYTAAHHTSLDQSSPPLSGTSPSYKYTLPGAQDAKDD
181			NK--KKALAHRLNHCT	SDPRWYGTQHSISLDQSSPPOSGVSTSYNHPVLGMYDAKDD
213	HDAC9a		FPLRKTASEPNLKVR	SRLKQKVAERRSSPPLRRKDGNNVTSFKKRMFEVTESSVSSSSSPG
213	HDAC9		FPLRKTASEPNLKVR	SRLKQKVAERRSSPPLRRKDGNNVTSFKKRMFEVTESSVSSSSSPG
213	HDAC4		FPLRKTASEPNLKVR	SRLKQKVAERRSSPPLRRKDGNNVTSFKKRMFEVTESSVSSSSSPG
239			FPLRKTASEPNLKVR	SRLKQKVAERRSSPPLRRKDGNNVTSFKKRMFEVTESSVSSSSSPG

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HDRP	273	SGPSSPNNGPTG	SVTENETSVLPPTPHAEOMVSOORILIHEDSMNLLSLYTSPSLPNITL
HDAC9a	273	SGPSSPNNGPTG	SVTENETSVLPPTPHAEOMVSOORILIHEDSMNLLSLYTSPSLPNITL
HDAC9	273	SGPSSPNNGPTG	SVTENETSVLPPTPHAEOMVSOORILIHEDSMNLLSLYTSPSLPNITL
HDAC4	298	SGPSSPNNGPTG	SVTENETSVLPPTPHAEOMVSOORILIHEDSMNLLSLYTSPSLPNITL
HDRP	333	GLPAVPSOLNAS	SLKEKOKCETOTLROGVPLPGOYGGSI PASSSHPHVTLECKPPNSSH
HDAC9a	333	GLPAVPSOLNAS	SLKEKOKCETOTLROGVPLPGOYGGSI PASSSHPHVTLECKPPNSSH
HDAC9	333	GLPAVPSOLNAS	SLKEKOKCETOTLROGVPLPGOYGGSI PASSSHPHVTLECKPPNSSH
HDAC4	357	GLPATGPSAGTAG	QQ-DTERLTLPALQQRISLFGTHLIPYLSIS--PLERDQ---GAAH
HDRP	393	OALLQHLLLLKE	OMROOKLLVAGG--VPLHPOSPLATKERISPGIRGTHKLPRHRPLNRTO
HDAC9a	393	OALLQHLLLLKE	OMROOKLLVAGG--VPLHPOSPLATKERISPGIRGTHKLPRHRPLNRTO
HDAC9	393	OALLQHLLLLKE	OMROOKLLVAGG--VPLHPOSPLATKERISPGIRGTHKLPRHRPLNRTO
HDAC4	411	SPLLQHMLLEQ	PPAQAPLVTCIGALPLHAQS-LVGADRVSF--SIHKLROHRPLGRTO
HDRP	451	SAPLPO--	STLAQLVIOOOHOOFLKOKO--YOOOIHMNKLLSKSIEOLKOPGSHLEAE
HDAC9a	451	SAPLPO--	STLAQLVIOOOHOOFLKOKO--YOOOIHMNKLLSKSIEOLKOPGSHLEAE
HDAC9	451	SAPLPO--	STLAQLVIOOOHOOFLKOKO--YOOOIHMNKLLSKSIEOLKOPGSHLEAE
HDAC4	467	SAPLPQNAQAL	QHVLVIOOOHOOFLKOKOQFQOOQIQMNKIIPKPSFEPARQFESHPEETE
HDRP	507	FEELQGD	OAMOE DRAPSSGNSTR--SDSSACVDDTLGOVGAVKVKEEPVDSDEDAOIOEMES
HDAC9a	507	FEELQGD	OAMOE DRAPSSGNSTR--SDSSACVDDTLGOVGAVKVKEEPVDSDEDAOIOEMES
HDAC9	507	FEELQGD	OAMOE DRAPSSGNSTR--SDSSACVDDTLGOVGAVKVKEEPVDSDEDAOIOEMES
HDAC4	527	FEELREH	QALLDEPYLDRLPQKATTAQAGVQVKQEPFIESDEEEAEPPREVFPQRQPSFQ
HDRP	566	GEOAAFM	OOVIGKDLAPGFMIKVII-----
HDAC9a	566	GEOAAFM	OOVIGKDLAPGFMIKVII-----
HDAC9	566	GEOAAFM	OOVIGKDLAPGFMIKVII-----
HDAC4	587	ELLFRQ	QALLLEQORIHOLRNYQASMEAGIPVSFGGHRPLSRQAQSSSPASATFPVSVQEP

FIG. 3B

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HD RP	626	PLQPGSATGIAYDPLMLKHOCVCGNSTIHPHAGRIOSIWSRLOETGLLNKCERI OGRKA
HD AC9a	626	PLQPGSATGIAYDPLMLKHOCVCGNSTIHPHAGRIOSIWSRLOETGLLNKCERI OGRKA
HD AC9	647	PTKRPRFTTGLVYDTLMLKHOCVCGNSTIHPHAGRIOSIWSRLOETGLLNKCERI OGRKA
HD AC4		
HD RP	686	SLEEIQLVHSEHSLLYGTNPLDGGOKLDPRIILGDDSOKEFFSSLPCCGGLGVSDTIWNEL
HD AC9a	686	SLEEIQLVHSEHSLLYGTNPLDGGOKLDPRIILGDDSOKEFFSSLPCCGGLGVSDTIWNEL
HD AC9	707	TLEELQTVHSEAHITLLYGTNPLNROKLDISKLLGSLASVFEVR-LPCGGIVGVSDTIWNEL
HD AC4		
HD RP	746	HSSGAARMAVGCVI ELASKVASGELKNGFAVVRPPGHHAEEESTAMGFCFFNSVAITAKYL
HD AC9a	746	HSSGAARMAVGCVI ELASKVASGELKNGFAVVRPPGHHAEEESTAMGFCFFNSVAITAKYL
HD AC9	766	HSAGAARILAVGCVVELVFKVATGELKNGFAVVRPPGHHAEEESTIPMGFCFFNSVAVAKILL
HD AC4		
HD RP	806	RDOLNISKILLVDLVHNGNGTOOAFYADPSILYISLHRYDEGNFFPGSGAPNEVRFISL
HD AC9a	806	RDOLNISKILLVDLVHNGNGTOOAFYADPSILYISLHRYDEGNFFPGSGAPNEVRFISL
HD AC9	826	QORLSVSKILLVDLWDVHNGNGTOOAFYISDPSVLYMSLHRYDDGNFFPGSGAPDEVGTGPG
HD AC4		
HD RP	866	EPHFYLYLSGNCITIA
HD AC9a	866	ECYNININIAWTCGLDPPMGDVEYIEAFRTIIVKPVAKKEFDPMVLVSAGFDALEGHTPTPLGG
HD AC9	886	VGFENVNMAFTGCLDPPMGDAEYIAAFRTIIVKPVAKKEFDPMVLVSAGFDALEGHTPTPLGG
HD AC4		
HD RP	926	YKVTAKCFGHLTKOLMILADGRVVLALLEGCHDLTAICDASEACVNALLGNEL EPIAEDITL
HD AC9a	946	YNLSARCFGYLT KOLMGLAGGRIVLALLEGCHDLTAICDASEACVSALLGNELDPIPEKVL
HD AC9		
HD AC4		
HD RP	986	HOSPNNNAVISLOKILIEIOSMSLKFS
HD AC9a	1006	QQRNANAVRSMEKQVMEIHSKYWRCLQRTTSTAGRSLIEAQTCENEEAEETVTAMASLSVG
HD AC9		
HD AC4		
HD RP		
HD AC9a		
HD AC9		
HD AC4	1066	VKPAEKRPDEEPEEPEPL

FIG. 3C

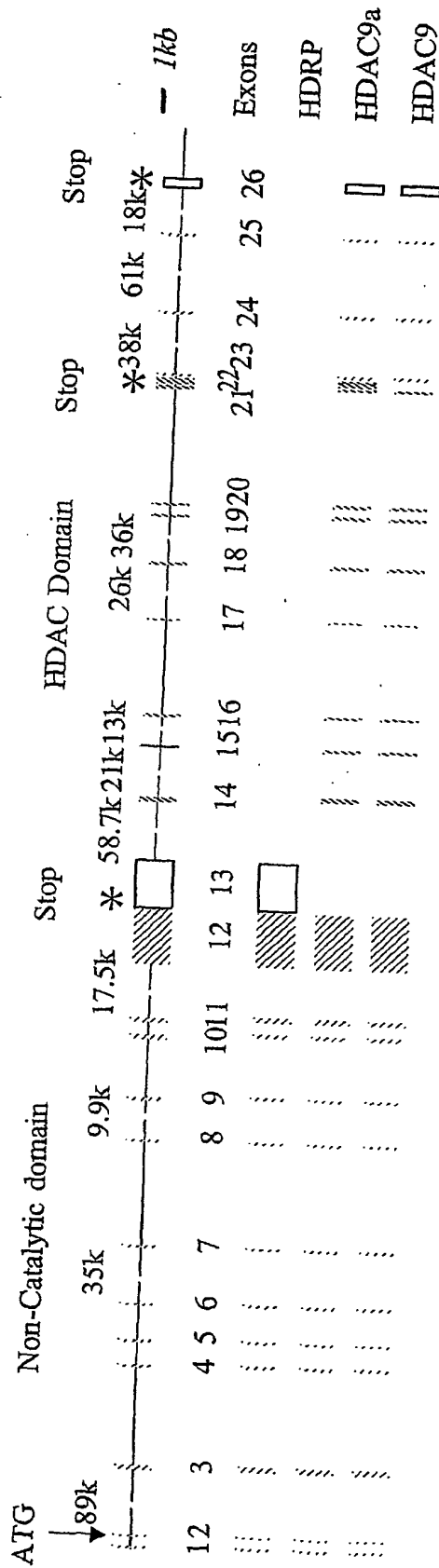


FIG. 4

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FIG. 5A
FIG. 5B
FIG. 5C
FIG. 5D

FIG. 5

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1 /¹ggggaagaga ggcacagaca cagataggag aagggcacgg gctggagcca cttgcaggac tgagggtttt tgcaacaaaa
ccctagcgc ctgaagaact

101 ctaagccag/²a tggggtggct ggaagagagc agctcttggc tcagcaaaga ATGCACAGTA TGATCAGCTC AGT/³GGATGTG
AAGTCAGAAG TTCCCTGTGGG

201 CCTGGAGCCC ATCTCACCCTT TAGACCCTAAG GACAGACCTC AGGATGATGA TGCCCGTGCTT GGACCCCTGTT GTCCGTGAGA
AGCAATTGCA GCAGGAATTA

301 CTTCTTATCC AGCAGCAGCA ACAATCCAG AAGCAGCTTC TGATAGCAGA GTTTCAGAAA CAGCATGAGA ACTTGACACG
GCAGCACCAG GCTCAGCTTC

401 AGGAGCATAT CAAG/⁴GAACTT CTAGCCATAA AACAGCAACA AGAACTCCTA GAAAGGAGC AGAACTGGA GCAGCAGAGG
CAAGAACAGG AAGTAGAGAG

501 GCATCGCAGA GAACAGCAGC TTCCTCCTCT CAGAGGCAA GATAGAGGAC GAGAAAG /⁵GGC AGTGGCAAGT ACAGAAGTAA
AGCAGAAGCT TCAAGAGTTC

601 CTACTGAGTA ATCAGCAAC GAAAGACACT CCAACTAATG GAAAAAATCA TTCCGTGAGC CGCCATCCCA AGCTCTGCTA
CAGG/⁶GCTGCC CACCACAT

701 CATTTGATCA AAGCTCTCCA CCCCTTAGTG GAACATCTCC ATCCTACAAG TACACATTAC CAGGAGCACA AGATGCAAAG
GATGATTTC CCCTTGAAA

FIG. 5A

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801 AACT/GCCTCT GAGCCCAACT TGAAGGTGG GTCCAGTTA AAACAGAAAG TGGCAGAGAG GAGAAGCAGC CCCTTACTCA
GGCGAAGGA TGGAAATGTT
 901 GTCATTTCAT TCAAGAAGCG AATGTTTGAG GTGACAG /⁸ AAT CCTCAGTCAG TAGCAGTTCT CCAGGCTCG GTCCCAGTTC
 ACCAAACAAT GGGCCAACCTG
 1001 GAAGTGTAC TGAATATGAG ACTTCGGTTT TGCCCCCTAC CCTCATGCC GAG /⁹ CAAATGG TTTCACAGCA ACGCAITCTA
 ATTCAATGAG ATTCCATGAA
 1101 CCTGCTAAGT CTTTATACCT CTCCTTCTTT GCCCAACATT ACCTTGGGGC TTCCCGCAGT GCCATCCCAG CTCATG /¹⁰ CTT
 CGAATTCACT CAAAGAAAAG
 1201 CAGAAGTGT AGAGGCAGAC GCTTAGGCAA GGTGTTCTC TGCCCTGGCA GTATGGAGC AGCATCCCG CATCTTCCAG
 CCACCTCAT GTTACTTTAG
 1301 AGGGAAGCC ACCCAACAGC AGCCACCAGG CTCCTCTGCA GCATTATTA TTGAAGAAC AAATGCGACA GCAAAGCTT
 CTTGTAGCTG /¹¹ GTGGAGTTCC
 1401 CTTACATCCT CAGTCTCCT TGGCAACAAA AGAGAGAATT TCACCTGGCA TTAGAGGTAC CCACAATTG CCCCCTCACA
 GACCCCTGAA CCGAACCAG
 1501 TCTGCACTT TGCCTCAGAG CAGTTGGCT CAGCTGGTCA TTCAACAGCA ACACCAGCAA TTCTTGGAGA AGCAGAAGCA
 ATACCAGCAG CAGATCCACA
 1601 TGAACHAA /¹² CT GCTTTCGAAA TCTATTGAAC AACTGAAGCA ACCAGGCAGT CACCTTGAGG AAGCAGAGGA AGAGCTTCAG
 GGGGACCAG CGATGCAGGA

FIG. 5B

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1701 AGACAGAGCG CCTCTAGTG GCAACAGCAC TAGGAGCGAC AGCAGTGCCT GTGTGGATGA CACACTGGGA CAAGTTGGGG
 CTGTGAAGGT CAAGAGGAA
 1801 CCAGTGGACA GTGATGAAGA TGCTCAGATC CAGGAATGG AATCTGGGA GCAGGCTGCT TTTATGCAAC AG
 /¹³GTAAATAGG CAAAGATTTA GCTCCAGGAT TTGTAATTAA AGTCATTATC TGA..... /¹⁴CCTTTCTT GGAACCCACG CACACAGGTG
 1901 CGCTCTCTGT GCGCCAAGCT CCGCTGGCTG CCGTGGCAT GGATGGATTA GAGAAACACC GTCTCGTCTC CAGGACTCAC
 TCTTCCCCCTG CTGCCCTCTGT
 2001 TTTACCTCAC CCAGCAATGG ACCGCCCCCT CCAGCCTGGC TCTGCAACTG /¹⁵GAATTGCCTA TGACCCCTTG ATGCTGAAAC
 ACCAGTGGGT TTGTGGCAAT
 2101 TCCACCACCC ACCCTGAGCA TGCTGGAGCA ATACAGAGTA TCTGTTCAG ACTGCAAGAA ACTGGGCTGC TAAATAATG
 TGAG/¹⁶CGAATT CAAGTTCGAA
 2201 AAGCCAGCTT GGAGGAATA CAGCTTGTTC ATTCTGAACA TCACTCACTG TTGTATGGCA CCAACCCCTT GGACGGACAG
 AAGCTGGACC CCAGGATACT
 2301 CCTAG/¹⁷GTGAT GACTCTCAA AGTTTTTTTTC CTCATTACCT TGTTGTGGAC TTGGG/¹⁸GTGGA CAGTGACACC ATTTGGAATG
 AGCTACACTC GTCCGGTGCT
 2401 GCACGGCATGG CTGTTGGCTG TGTATCGAG CTGGCTTCCA AAGTGGCCTC AGGAGAGCTG AAGA /¹⁹ATGGGT TTGCTGTTGT
 GAGGCCCTT GGCCATCAGG
 2501 CTGAAGAATC CACAGCCATG /²⁰GGGTCTCTGCT TTTTAAATTC AGTTGCAATT ACCGCCAAT ACTTGAGAGA CCAACTAAT
 ATAGCAAGA TATTGATTGT

FIG. 5C

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2601 AGATCTG/²¹GAT GTTCACCATG GAAACGGTAC CCAGCAGGCC TTTTATGCTG ACCCCAGCAT CCTGTACATT TCACTCCATC
 GCTATGATGA AGGGAACTTT
 2701 TTCCCTGGCA GTGGAGCCCC AAATGAGG/²²TT CGGTTTATTT CTTTAGAGCC CCACTTTTAT TTGTATCTTT CAGGTAATTG
 CATTGCATGA ttacccctaa
 2801 ttttcttgtc ctttgctggt gttttaaatt acacgagatt actgaattgt cccatgggac caagaaccag tgcagaacaa
gtgcataacc cagagcactg
 2901 tttgtcaggg aaggttgggc tgatttgatg tgbtggttga tgtttatttc aagagctccc atgtgcttgt tttctctctc
tcttgcttct ttcacatttgc
 3001 tctcttctct gcccacctg gtgtgtcttt ctcttcccag /²³gttgaacag gccttggaagg aggttacaat ataaatattg
 cctggacagg tggccttgat
 3101 cctcccatgg gagatgttga gtaccttgaa gcattcag/²⁴ga ccategtgaa gcctgtggcc aaagagtttg atccagacat
 ggtcttagta tctgctggat
 3201 ttgatgcatt ggaaggccac accctctctc taggagggtta caaagtgaag gcaaaatg/²⁵tt ttggtcattt gacgaagcaa
 ttgatgacat tggctgatgg
 3301 acgtgtgggtg ttggctcttag aaggaggaca tgatctcaca gccatctgtg atgcacaga agcctgtgta aatgccttc
 taggaaatga g/²⁶ctggagcca
 3401 cttgcagaag atattctcca ccaaagcccg aatatgaatg ctgttatttc ttacagaag atcattgaaa ttcaaatat
 gtctttaaag ttctcttaa.....

FIG. 5D

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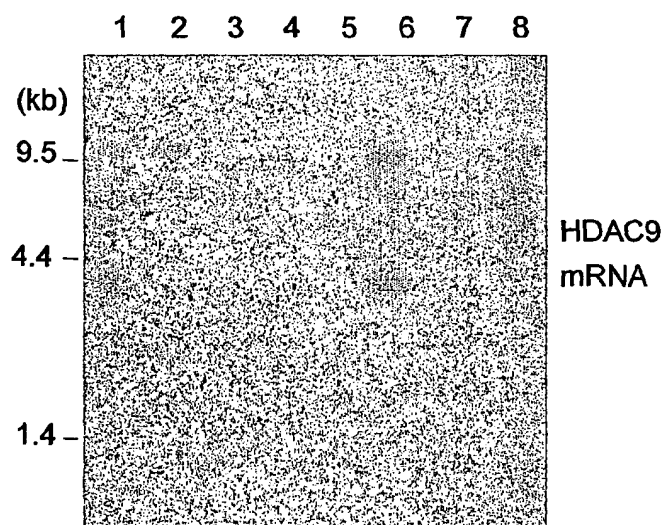


FIG. 6A

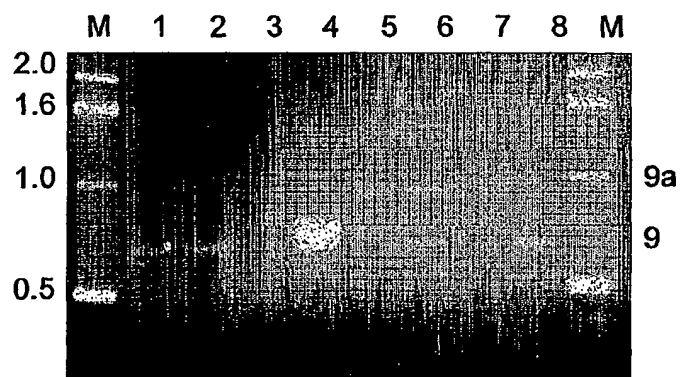


FIG. 6B

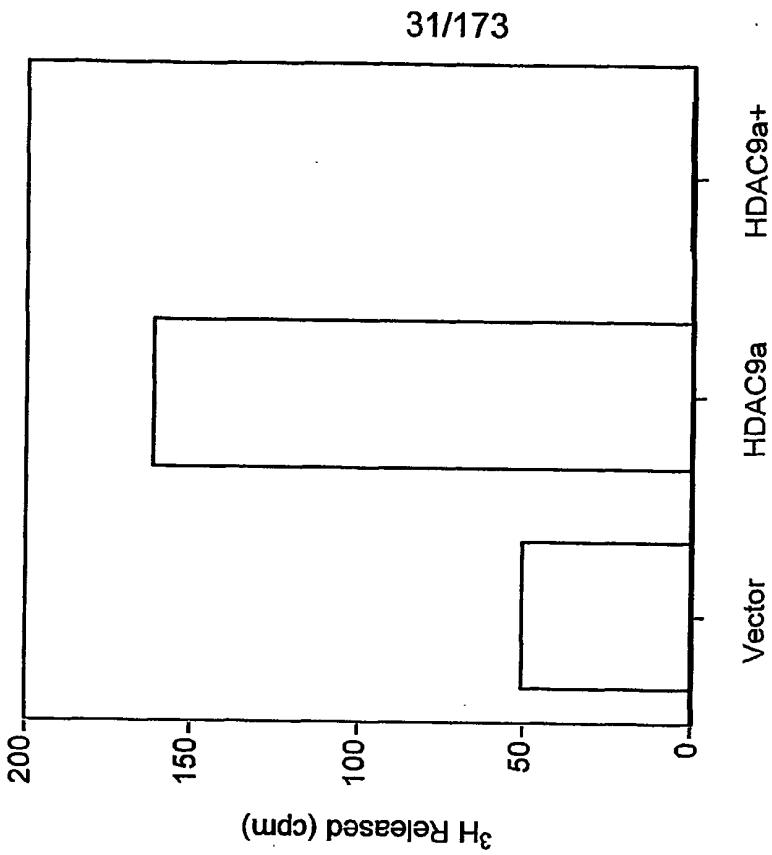


FIG. 8

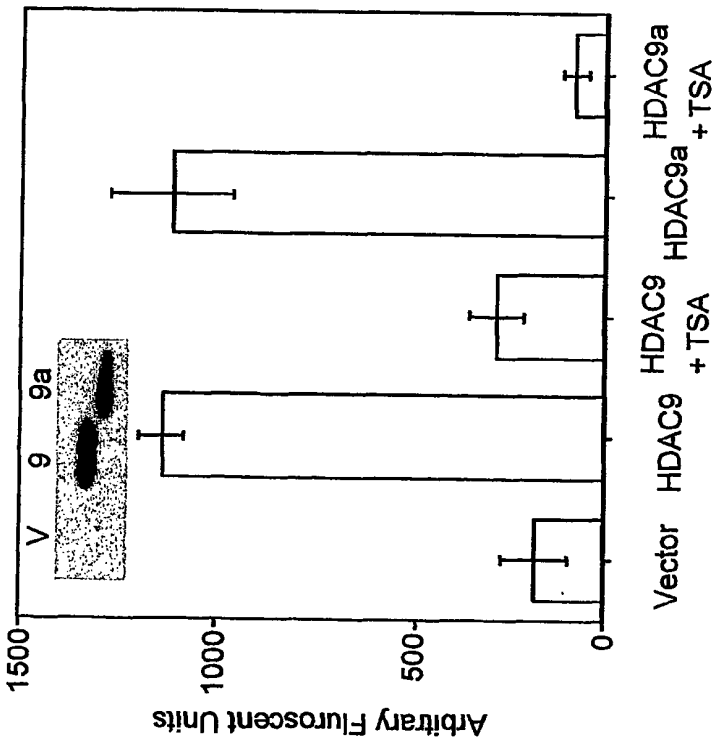


FIG. 7

FIG. 9A

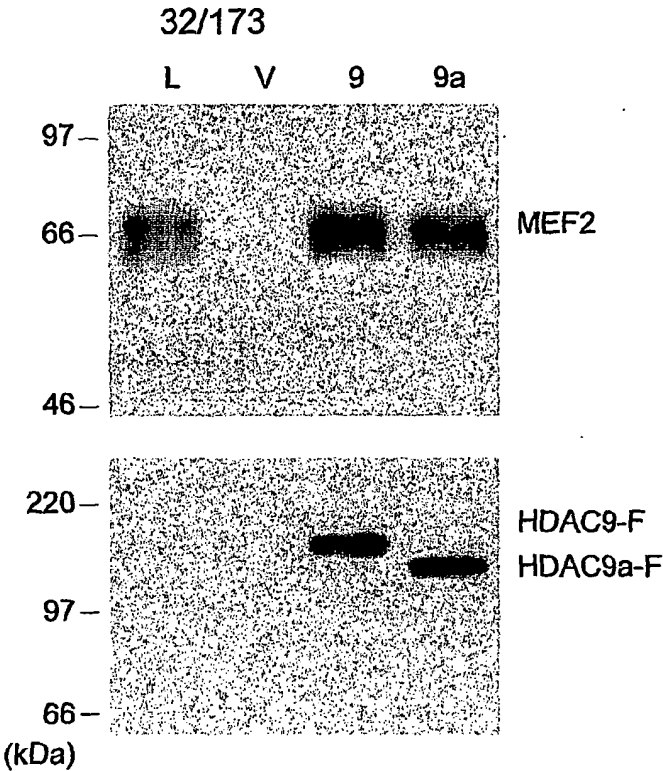
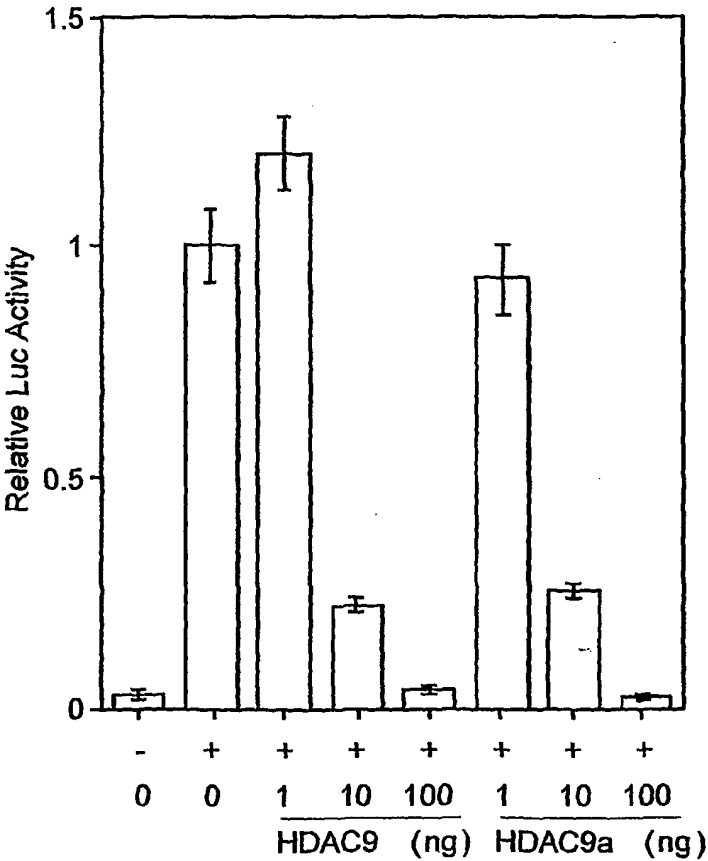


FIG. 9B



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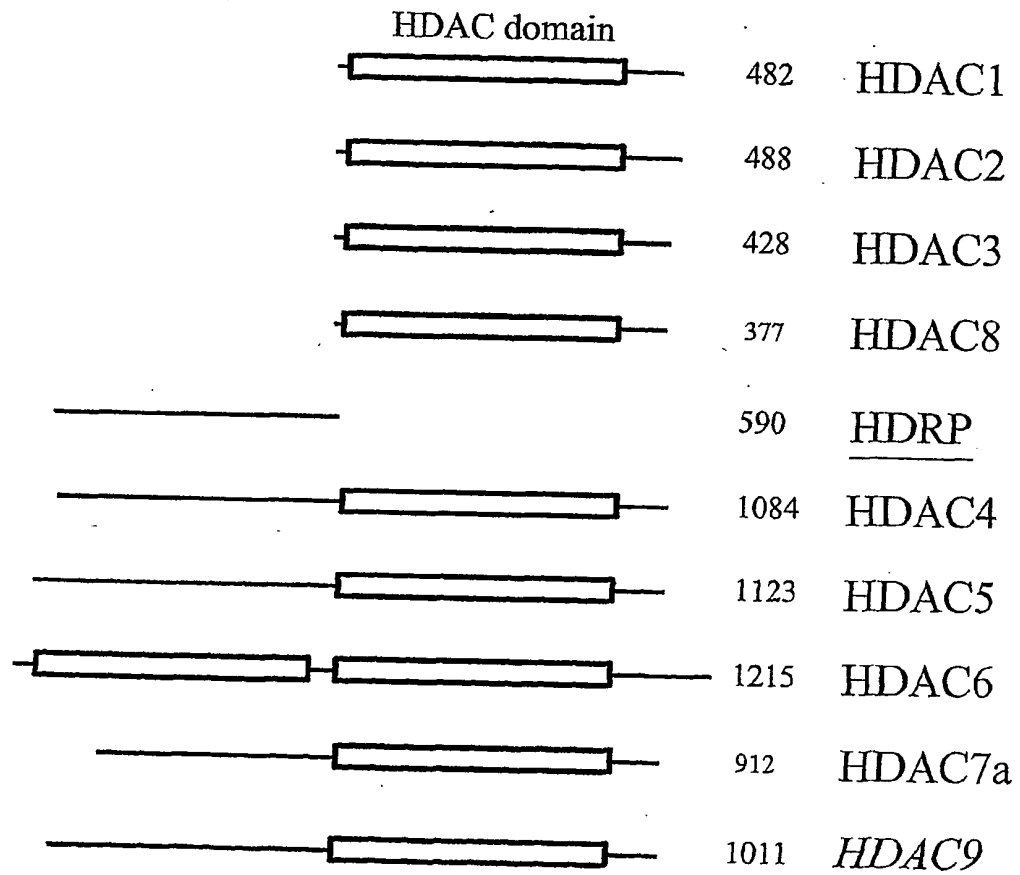


FIG. 10

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FIG. 11A
FIG. 11B
FIG. 11C
FIG. 11D
FIG. 11E
FIG. 11F

FIG. 11

FIG. 11A

cccatcggccattcaggctgcgcaactgttgggaaggcgatcgggtgcggccctctcgctattaccgagctggcgaaaggg
ggatgtgctgcaaggcgattaaagtgggtaacgcccagggtttccagtcacgacgttgtaaaaacgacggccagtgccaagct
gatctaataatcaatattggccattagcccatattattcattggttatatagcataaataatggtctattggccattgcatacgttgatcca
tatcataataatgtacatttatattggtcatgtctcaacattaccgcatgttgacattgattattgactagttattaatagtaataattacg
gggtcattagttcatagcccataatggagttccgcgttacataacttacggtaaatggcccgctggcgaccccgagccgagccc
ccggccgttgacgtcaatagtgacgtatgttcccatagtaacgccaatagggaacttccattgacgtcaatgggtggagtatttacg

gtaaactgcccacttggcagtagacatcaagtgtatcatatgccaaagtcccccctattgacgtcaatgacggtaaatggcccgcct
 agcattatgccagtagacatgaccttacgggaggttctactacttggcagtagacatctacgtattagtcacgtctattaccatgggtgatcgg
 gtttggcagtagacaccaatggcgtggatagcggtttgactcaggggatttccaagtctccacccattgacgtcaatgggaggtt
 tgttttggcaccaaaatcaacgggactttccaaaatgtcgaataacccccgggttgacgcaaatggcggtagggcgtgtgtacg
 gtgggaggtctatatataagcagagctcgttttagtgaaaccgtcagaattcaagcttggcgccgagatctatcgtcagggatatac
 (EcoRV)
acc

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ATGCACAGTATGATCAGCTCAGTGGATGTGAAGTCAGAAAGTTCTGTGGG
 CCTGGAGCCCATCTCACCTTTAGACCTAAGGACAGACCTCAGGATGATGA
 TGCCCCGTGGTGAACCTGTTGTCCGTGAGAAAGCAATTGCAGCAGGAATTGA
 CTTCTTATCCAGCAGCAGCAACAATCCAGAAGCAGCTTCTGATAGCAGA
 GTTTCAGAAACAGCATGAGAACTTGACACCGCAGCACCCAGGCTCAGCTTC
 AGGAGCATATCAAGGAACTTCTAGCCATAAACAAGCAACAAGAACTCCTA
 GAAAAGGAGCAGAAACTGGAGCAGCAGAGGCAAGAAACAGGAAAGTAGAGAG
 GCATCGCAGAGAACAGCAGCTTCTCCTCTCAGAGGCAAGATAAGAGGAC
 GAGAAAGGCAGTGGCAAGTACAGAAAGTAAAGCAGAAAGCTTCAAGAGTTC
 CTACTGAGTAAATCAGCAACGAAAGACACTCCAATAATGGAAAAAATCA
 TTCCGTGAGCCGCCATCCCAAGCTCTGGTACACGGCTGCCACCAACAT
 CATTGGATCAAGGCTCTCCACCCCTTAGTGGAACATCTCCATCCTACAAG

FIG. 11B

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TACACATTACCAGGAGCACAAAGATGCAAAGGATGATTTCCCCCTTCGAAA
AACTGCCCTCTGAGCCCAACTTGAAGTGCGGTCCAGGTTAAACAGAAAG
TGGCAGAGAGGAGAAGCAGCCCCCTTACTCAGGCGAAGGATGGAATGTT
GTCACTTCATTCAAGAAGCGAATGTTTGAGGTGACAGAAATCCTCAGTCAG
TAGCAGTTCTCCAGGCTCTGGTCCCAGTTACCAAACAATGGCCAACTG
GAAGTGTTACTGAAAAATGAGACTTTCGGTTTTCGCCCTACCCCTCATGCC
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ACACCAGCAATTCTTGAGAGAGCAGAAGCAATACCAGCAGCAGATCCACA
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GTGTGGATGACACACTGGGACAAGTTGGGGCTGTGAAGTCAAGGAGGAA
CCAGTGGACAGTGATGAAGATGCTCAGATCCAGGAAATGGAATCTGGGGA
GCAGGCTGCTTTTATGCAACAGCCTTTCCTGGAACCCACGCACACACGTG
CGCTCTCTGTGCGCCAAGCTCCGCTGGCTGGCTTGGCATGGATGGATTA

FIG. 11C

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GAGAAACACCGTCTCGTCTCCAGGACTCACTCTTCCCCTGCTGCCTCTGT
TTTACCTCACCCAGCAATGGACCGCCCCCTCCAGCCTGGCTCTGCAACTG
GAATTGCCCTATGACCCCTTGATGCTGAAACACACAGTGCCTTTGTGGCAAT
TCCACCAACCCCTGAGCATGCTGGACGAATACAGAGTATCTGGTCACG
ACTGCAAGAAACTGGGCTGCTAAATAAATGTAGCGAAATTC AAGGTCGAA
AAGCCAGCCTGGAGGAAATACAGCTTGTTCATCTGAACATCACTCACTG
TTGTAITGGACCAACCCCTGGACGGACAGAAAGCTGGACCCAGGATACT
CCTAGGTGATGACTCTCAAAAGTTTTCCTCATTAACCTTGTGGTGGAC
TTGGGTGGACAGTGACACCATTTGGAAATGAGCTACACTCGTCCGGTGCT
GCACGATGGCTGTTGGCTGTGTCACTGAGCTGGCTTCCAAAGTGGCCTC
AGGAGAGCTGAAGAAATGGGTTTGCTGTGTGAGGCCCCCTGGCCATCAG
CTGAAGAAATCCACAGCCATGGGTTCTGCTTTTAAATTCAGTTGCAATT
ACCGCCAAATACTTGAGAGACCAACTAAATATAAGCAAGATATTGATTGT
AGATCTGGATGTTCAACCATGGAAACGGTACCAGCAGGCCCTTTTATGCTG
ACCCAGCATCCTGTACATTTCACTCCATCGCTATGATGAAGGAACTTT
TTCCCTGGCAGTGGAGCCCCAAATGAGGTTGGAACAGGCCCTTGGAGAGG
GTACAAATATAATATTGCCCTGGACAGGTGGCCTTGATCCTCCATGGGAG
ATGTTGAGTACCTTGAAGCATTCAGGACcaTCGTGAAGCCTGTGGCCAAA
GAGTTGATCCAGACATGGTCTTAGTATCTGCTGGATTTGATGCATTGGA
AGGCCACACCCCTCCTAGGAGGGTACAAAGTGACGGCAAAATGTTTGTG
GTCAATTGACGAAGCAATTGATGACATTTGGCTGATGGACGTTGTGTGTG
GCTCTAGAAGGAGGACATGATCTCACAGCCATCTGTGATGCATCAGAAGC
CTGTGTAATGCCCTTCTAGGAAATGAGCTGGAGCCACTTGCAGAAAGATA
TTCCTCCACCAAGCCCCGAATATGAATGCTGTTATTTCTTTTACAGAAGATC
ATTGAAATTCAAAGTATGTCTTTAAAGTTCTCT

FIG. 11D

FIG. 11E

(BamHI)ggatccgggtacacagattacaaggagacgacgagatgacaaagtatgacccggggggtggtcatccctgtgacccctcccccagtg
ccctctctgggcccgttgaaagtggccactccagtgccccacacgccccttgctcctaataaaaattaaagtggcatcatttgctgactagtggtgctc
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aat

FIG. 11F

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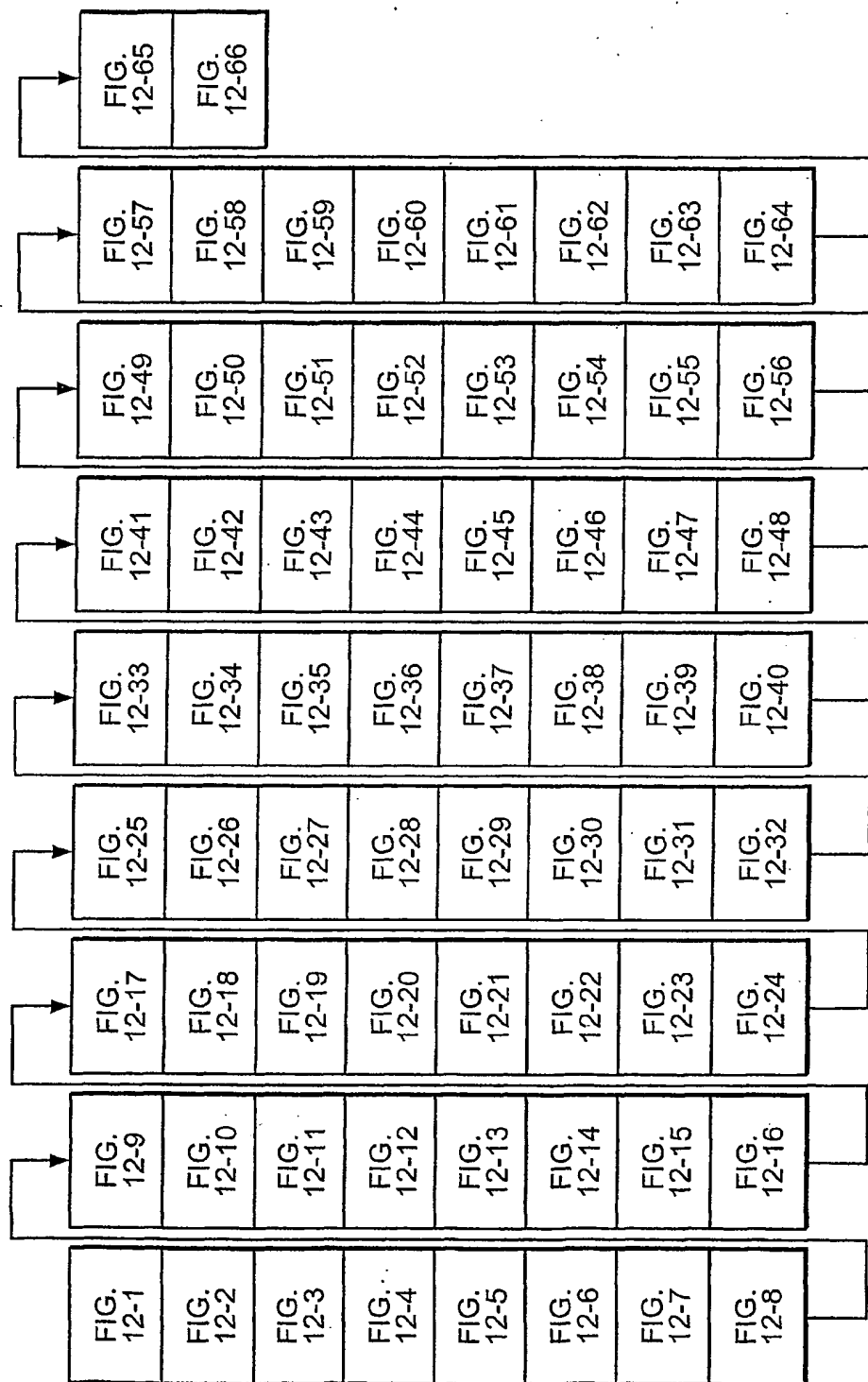


FIG. 12

pFLAG-CMV-5b-HDAC9

7699 base pairs

Graphic map | Table by enzyme name

AviII	BstMCI	EarI	MspAII
BglI	PvuI	Eam1104I	PvuII
FspI	BsaOI		
cccatcgccattcaggctgcgcaactgttgggaaggcgatcggtgcgggcctcttcgctattacgccagctgg			
base pairs			
gggtaagcggtaagtcgacgcggttgacaaaccttcccgcgtagccacgcccggagaagcgataatgcggtcgacc			
1 to 75	Acc16I	BspCI	NspBII
		Bsh1285I	
		Ple19I	
		Ksp632I	

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cgaaagggggatgtgctgcaaggcgatttaagttgggtaacgcccagggtttcccagtcacgacgttgtaaaacg
base pairs
gctttccccctacacgacgttccgcctaattcaacccattgcgggtcccaaaagggtcagtgctgcaacatttgc
76 to 150

FIG. 12-1

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	MsCI	
	CfrI	
	SspI MluNI	
EaeI		
acggccagtgccaagctgatctaataatcaatatattggccattagccataattattcattggttatatatagcataaatcaa		
base pairs		
tgcgggtcacgggttcgactagattagttataaaccggtaatcgggtataaagaaccaataatatcgtatttagtt		
151 to 225		
CfrI	EaeI	
	BalI	
	MsCI	
	MluNI	
SspI	EaeI	SspBI
	BsrDI	Bsp1407I
tattggctattggccattggcattacgttgtatccataatcataaataatgtacatttatattggctcatgtccaacatt		
base pairs		
ataaccgataaaccggtaacgtatgcaacatagggtatagttatatcatgtataataaaccgagtagcagggttgtaa		
226 to 300		
CfrI		BsrGI
	BalI	

FIG. 12-2

HincII VspI
 SpeI PshBI
 accgccatgttgacattgattattgactagttatttaataagtaatcaattacggggtcatttagttcatagcccata
 base pairs
 tggcggtaacaactgtaactaataactgatcaataattatcattagttaatgccccagtaatcaagtatcgggtat
 301 to 375
 HindII AclNI AsnI
 AseI

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BstMCI HincII
 AcyI
 tatggagttccgcgttacataacttacggtaaatggcccgccctggcgaccgccccagcgaccccccgcttgacg
 base pairs
 atacctcaaggcgcaatgtattgaatgccattaccggcgaccgctggcgggtcgctggggcgggcaactgc
 376 to 450
 BglI BsaOI HindII
 Bsh1285I
 BsiEI

FIG. 12-3

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```
AatII      BbiII
BbiII      BbiII
BbiII      BbiII
tcaatagtgacgtatgttcccatagtaacgccaatagggaacttccattgacgtcaatgggtggagtatttacgg
base pairs
agttatcactgcatacaagggtatcattgcgggttatccctgaaaggtaactgcagttaccacacctcataaatgcc
451 to 525
Hsp92I      Msp17I
            BsaHI
            Hsp92I

            BbiII
            HinII
            AcyI AatII

            BglI      NdeI
            taaactgcccacttggcagtagcatcaagtgtatcatatgcccaagtcgcgccttatcgacgtcaatgacggtaaa
            base pairs
            atttgacgggtgaaccgtcatgttagttcacatagtagtgcgggttcaggcgggggataaactgcagttactgccattt
            526 to 600

            FauNDI
            Msp17I
            BsaHI
            Hsp92I
```

FIG. 12-4

BstSNI
SnaBI
tggccgcctagcattatgccccagtagcatgaccttacgggagtttcctacttggcagtagcatctacgtattagtc
base pairs
accgggcgggatcgtaataacgggtcatgtactgggaatgccctcaaggatgaaccgtcatgtagatgcataatcag
601 to 675

BsaAI
Eco105I

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NcoI Bsp19I
StyI BstDSI
EcoT14I

atcgctattaccatgggtgatgcgggttttggcagtagacaccaaatgggcgtggatagcgggtttgactcacggggattt
base pairs
tagcgataatgggtaccactacgcccacaaacgcgtcatgtggttaccgcacctatcgccaaactgagtgcctctaaa
676 to 750

BssT1I
ErhI Eco130I
DsaI MslI

FIG. 12-5

BbiII	AccB1I		
Hin1I	BshNI		
ACyI AatII			
ccaagtctccacccattgacgtcaatgggagtttgtttggcaccaaaatcaacgggactttccaaaatgtcgt			
base pairs			
99ttcagaggtgggtaactgcagttaccctcaaaaaccgtggttttagttgcccctgaaaggttttacagca			
751 to 825			
Msp17I	BanI		46/173
BsaHI	Eco64I		
Hsp92I			
HincII	BanII		
aataaccccgcccggttgacgcaaatgggcggtaggcgtgtacggtgggaggtctatataagcagagctcgttta	Eco24I		
base pairs	EcoICRI		
ttattggggcgggcaactgcggtttaccggcccatccgcacatgccaccctccagatatattcgtctcgagcaaat			
826 to 900			
HindII	Ecl136II		
	SacI		

FIG. 12-6

FIG. 12-7

gatgatgatgcccggtggtggaccctgttgcgtgagaagcaattgcagcaggaattacttcttatccagcagca
base pairs
ctactactacggggcaccacctgggacaaacaggcactcttcgttaacgtcgtccttaatgaagaataggtcgtcgt
1051 to 1125

DsaI DrrI MfeI Asp700I
BstDSI MunI XmnI

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FIG. 12-8

AlwNI
 gcaacaaatccagaagcagcttctgatagcagagtttcagaaacagcatgagaacttgacacggcagcaccaggc
 base pairs
 cggtggttaggtcttcgtcgaagactatcgtctcaagtccttctgtcgtaactcttgaaactgtgccgtcgtggtccg
 1126 to 1200

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BlpI	Eco57I	EcoNI	AlwNI
CelII			
tcagcttcaggagcatatcaaggaaacttctagccataaaacagcaacaagaactcctagaaaaggagcagaaact			
base pairs			
agtcgaagtcctcgtatagttccttgaagatcgggtatttctgtcgttgttcttgaggatcttttcctcgtcttga			
1201 to 1275			
Bsp1720I			
Bpu1102I			

FIG. 12-9

BpmI
ggagcagcagaggcaagaacaggaaagtagagaggcatcgagagagaacagcagcttcctcctcagagggcaaga
base pairs
cctcgtcgtctcctggttccttcattcctccgtagcgtctctgtcgtcgaaggaggagagtcctccggttct
1276 to 1350
GsuI

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EcoNI

HindIII
tagaggacgagaaaggcagtggaagtagacagaaagtaaacag aagcttcaagagttcctactgagtaaatcagc
base pairs
atctcctgctcttcccgtcaccggttcattgtcttcatttcgtc ttcgaagttctcaaggatgactcatttagtcg
1351 to 1425

FIG. 12-10

Van91I
 AccB7I
 aacgaaagacactccaactaatggaaaaaatcattccgtgagccgcatcccaagctctggtacacggctgcccc
 base pairs
 ttgctttctgtgaggttgattaccttttttagtaaggcactcggcggtagggttcgagaccatgtgccgacgggt
 1426 to 1500

Esp1396I
 PflMI
 51/173

Van91I
 AccB7I
 ccacacatcattggatcaaagctctccacccttagtggaacatctccatcctacaagtacacattaccaggagc
 base pairs
 ggtgtgtagtaaacctagtttcgagaggtgggggaatcaccttgtagaggtaggatgttcatgtgtaatgggtcctcg
 1501 to 1575

FIG. 12-11

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Alw21I	BstBI		
AspHI	Bpu14I	FriOI	
	Csp45I	Eco24I	
acaagatgcaaaaggatgattcccccttcgaaaaactgcctctgagcccaacttgaaggcggtccagggttaaa			
base pairs			
tgttctacgtttcctactaaaggggaagctttttgacggagagactcgggttgaaacttccacgccagggtccaattt			
1576 to 1650			
BsiHKAI	SfuI Bsp119I	BanII	
Bbv12I	NspV		
	LspI		
	BseRI	EcoNI	
acagaaaagtggcagagaggagaagcagcccccttactcaggcggaaggatggaaatgttgtcattcattcaagaa			
base pairs			
tgtctttcacccgtctctcctcttcgtcgggggaatgagtcgcgccttcctacacctttacaacagtgaaagtaagtctt			
1651 to 1725			

FIG. 12-12

Van91I	Van91I
AccB7I	AccB7I
BpmI PflMI	
gcgaatgtttgaggtgacagaatcctcagtcagtagcagttctccaggctctggtcccagttcaccaaaatgg	
base pairs	
cgcttacaactccactgtcttaggagtcagtcacgaggtccgagaccagggtcaagtggttgttacc	
1726 to 1800	

Esp1396I
PflMI

GsuI
Esp1396I
AlwNI

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gccaaactggaagtgttactgaaaatgagacttcggttttgccccctaccctcatgccgagcaaatggtttcaca
base pairs
cggttgaccttcacaatgacttttactctgaagccaaaacgggggatggggagtagcggtcgtttaccaaaagtgt
1801 to 1875

FIG. 12-13

BsaMI
 Mva1269I
 gcaacgcattcttaattcatgaagattccatgaacctgctaagtctttatacctctccttcttgcacattac
 base pairs
 cgctgcgtaagattaaagtacttctaagggtacttggacgattcagaaatatggagaggaagaaacgggttgtaatg
 1876 to 1950
 BsmI RcaI
 BspHI

XcmI

BspMI

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ErhI
 BssT1I
 cttggggcttcccgcagtgccatcccagctcaatgcttc gaattcactcaagaaagcagaagtgtgagacgca
 base pairs
 gaacccgaaagggcggtcacggtagggcgagttacgaag ctttaagtgaagtcttcttgcgtcttcacactctgcgt
 1951 to 2025
 EcoT14I
 SfuI Bsp119I
 BsmBI
 NspV ApoI
 LspI EcoRI

FIG. 12-14

55/173

gacgcttaggcaaggtgttcctctgcctgggcagtatggaggcagcatcccgcatcttccagccacctcatgt
base pairs
ctgcgaatccggtccacaaggagacggaccggtccgtcgtagggccgtagaaggtcgggtgggagtaca
2026 to 2100

MslI

tactttagagggaagccaccaaacagcagcaccagggtctc ctgcagcatttattattgaaagaacaaatgcg
base pairs
atgaaatctccctttcgggtgtcgtcgggtgggtccgagag gacgtcgtaataataactttcttggtttacgc
2101 to 2175

PstI

SfiI

BstSFI

FIG. 12-15

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HindIII	Eco130I	StyI	ApoI
acagcaaaagcttctttagctggagggtcccttacatcctcagtcctcccttggaacaaagagagaatttc			
base pairs			
tgtcgttttcgaagaacatcgaccacctcaaggggaatgtaggagtcagaggggaaccgttggtttctctcttaaaag			
2176 to 2250			
	BssTII	ErhI	AcsI
Asp718I			
Acc65I			
BshNI			BsgI
acctggcattagaggtacccacaaaattgccccgtcacagacccctgaaccgaaccagtcctgcacctttgcctca			
base pairs			
tggaccgtaatctccatgggtgtttaacggggcagtgctctggggacttggtctgggtcagacgtggaaacggaggt			
2251 to 2325			
	BanI	KpnI	
	AccB1I		
	Eco64I		

FIG. 12-16

Bpu1102I
 Alw21I Bsp1720I
 Asphi CelII
 gagcagttggctcagctgggtcattoaacagcaacaccagcaattcttggaagcagaagcaataaccagcagca
 base pairs
 ctcggtgcaaccgagtcgaccagtaagttgtcggttggtcggttaagaacctcttcgtcttcggttatgggtcgtcgt
 2326 to 2400
 BsiHKAI PvuII
 Bbv12I B1pI MspA1I
 NspBII

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MflI
 XhoII
 gatccacatgaacaaactgcttttcgaaatctattgaacaactgaagcaaccaggcagtcaccttgagggaagcaga
 base pairs
 ctagggtgtacttggttgacgaaagcttttagataacttggtgacttcggttggtccggtcagtggaactcccttcgtct
 2401 to 2475
 BstYI
 BstX2I
 BstBI
 Bpu14I
 Csp45I
 Eco57I
 SfuI Bsp119I
 NspV
 LspI

FIG. 12-17

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EarI
 Bam1104I
 Asp700I
 Bbv16II
 BbsI Bsp143II
 ggaagagcttcaggggaccagggcgatgcaggaagacagagcgccctctagtggaacagcactaggagcgacag
 base pairs
 ccttctcgaagtccccctggtcgctacgtccttctgtctcgcgggagatcacccgttgcgtgatccctcgctgtc
 2476 to 2550

XmnI Eco57I
 Ksp632I
 SspI
 BpiI HaeII
 BpuAI BstH2I

BcgI
 cagtgccttgcgtggatgacacactgggacaaagtggggctgtgaagggtcaaggagggaaccagtggaacagtgatga
 base pairs
 gtcacgaacacacactactgtgtgaccctgttcaaccccgacacttccagttcctccttggtcacctgtcactact
 2551 to 2625

FIG. 12-18

MflI Van91I
 XhoII AccB7I
 agatgctcagatccaggaaatggaatctggggagcaggctgcttttatgcaacagcctttcctggaacccacgca
 base pairs
 tctacgagtcctaggtcctttaccttagacccctcgtccgacgaaaaatacgttggtcggaaggaccttgggtgcgt
 2626 to 2700
 BstYI Esp1396I
 BstX2I PflMI

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PmaCI
 PmlI
 AflIII
 NspBII
 Esp3I
 cacacgtgcgctctctgtgcgccaagctccgctggctgcggttgccatggatggattagagaaacacgcgtctcgt
 base pairs
 gtgtgcacgcgagagacacgcggttcgaggcgaccgacgccaacccgtacctaatactcttctgtggcagagca
 2701 to 2775
 MslI Eco72I
 MspAII
 BsmBI
 BsaAI
 BbrPI

FIG. 12-19

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	EaRI		BsrDI	BpmI
	Eam1104I			
ctccaggactcactot	ttccccctgctgcctctgttt	tacctcaccagcaatggacgcgcctccagcctggctc		
base pairs				
gaggtcctgagtgagaagg	ggacgacggagacaaaatggagtgggtcggttacctggcgggggaggtcgggaccgag			
2776 to 2850				
GsuI	Ksp632I			GsuI

	XcmI
tgcaactggaattgcctatgacccttgatgctgaacacacagtcggtttgtggcaattccaccaccacctga	
base pairs	
acgttgacccttaacggatactggggaactacgactttgtggtcacgcaaacacccgttaaggtggtgggtgggact	
2851 to 2925	

FIG. 12-20

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AggTcGaaAagCcagCctGgagGaaAtacagCctTgtTcattctGaaCatcactcactgtTgtatggcaccaacc
base pairs
tccagcttttcggtcggacctccttttatgtcgaaCaagtaagacttTgtagtgaTgacaacataccgtggttggg
3001 to 3075

AccB1I
BshNI
BpmI
GsuI
BanI
Eco64I

FIG. 12-21

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ErhI
StyI Eco130I
ECOT14I
BstXI AlwNI
cctggacggacagaagctggaccccaggatactcctagtgatgactctcaaaagttttttcctcattaccttg
base pairs
ggacctgacctgtcttcgacctg999gtccctatgaggatccactactgagagttttcaaaaaaggagtaatggaac
3076 to 3150

BsST1I
AvrII
BlnI

BsaWI BsgI
tggaggacttggggtggacagtgacaccatttggaaatgagctacactcgctcgggtgctgcacgcacatggctgttg
base pairs
accacctgaacccccacctgtcactgtggtaaaccttactcgatgtgagcaggccacgacgtgcgtaccgacaacc
3151 to 3225

FIG. 12-22

CvnI	Eco57I	CfrI
AocI		DraII EaeI
Bsu36I		
ctgtgtcatcgagctggcttccaaagtggcctcaggagagctgaagaatgggttgctgtgtgagggcccttg		
base pairs		
gacacagtagctcgaccgaagggtttcacccggagtcctctcgacttcttaccacaaacgacacactccgggggacc		
3226 to 3300		
Eco81I	Eco0109I	
Bse21I		

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MscI	ErhI Eco130I
	BstXI
	Eco57I MslI DsaI
ccatcacgctgaagaatccacagccatgggttctgctttttaattcagttgcaattaccgccaatacttgag	
base pairs	
ggtagtgcgacttcttaggtgtcggtaccccaagacgaaaaaattaagtcaacgttaatggcggtttatgaactc	
3301 to 3375	
MluNI	EcoT14I
BalI	StyI BstDSI
	NcoI Bsp19I

FIG. 12-23

BstX2I NcoI Bsp19I Asp718I SseBI
 BstYI StyI BstDSI AccB1I
 Eco147I
 XhoII EcoT14I BshNI StuI
 BsaI agacaaactaaataagcaagatatgtgattgtagatctggatgttcaccatggaaacggtaccagcaggcctt
 base pairs tctggttgatttatattcgttctataactaacatctagaccctacaagtggtagccttggccatgggtcgtccggaa
 3376 to 3450
 Eco31I BglII Bst1I BanI KpnI AatI
 MflI ErhI Eco130I Eco64I Pme55I
 DsaI Acc65I

SspBI	MslI	Asp700I
Bsp1407I		
ttatgctgacccagcatcctgtacatttcactccatcgctatgatgaagggaactttttccctggcagtgaggc		
base pairs		
aatacgactggggctgtaggacatgtaaagtgaggtaggcatactacttcccttgaaaaaggaccgtcacctcg		
3451 to 3525	BsrGI	XmnI

FIG. 12-24

AatI StyI
Pme55I Eco130I
EcoT14I

NcoI Bsp19I
StyI BstDSI
BsaMI
MscI
MluI
AspI

EcoT14I	Mva1269I	EaeI	AtsI
catgggagatgttgagtaccttgaagcattcaggaccatcgtgaagcctgtggccaaagagtttgatccagacat			
base pairs			
gtaccctctacaactcatggaacttcgtaagtcctggtagcacttcggacacccggttctcaaaactaggctctgta			
3601 to 3675			
BssT1I	BsmI	CfrI	Tth111I
DsaI			
ErhI Eco130I		BalI	

FIG. 12-25

FIG. 12-26

Mph1103I
 EcoT22I
 Ppu10I
 BpmI
 tgatctcacagccatctgtgatgcatacagaagcctgtgtgtaaatgcccttctaggaatgagctggagccacttgc
 base pairs
 actagagtgtcggtagacactacgtagtcttcggacacatttacgggaagatcctttactcgaccctcggtgaacg
 3826 to 3900
 NsiI
 Zsp2I
 GsuI

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Asp700I
 BsaMI
 Mva1269I
 ApeI
 agaagatatctccaccacccgaatatgaatgctgttatctttacagaagatcattgaaattcaaagtat
 base pairs
 tcttctataagaggtggttccgggttatacttacgacaataaagaaatgtcttctagtaactttaagtttcata
 3901 to 3975
 XmnI
 BsmI
 AclI

FIG. 12-27

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FIG. 12-28

AspEI DraII
 Eam1105I PspOMI
 SspI
 aagttgcatcattttgtctgactagggtgtcctctataattatggggtggaggggggtgtatggagcaagggg
 base pairs
 ttcaacgtagtaaaacagactgatccacaggagatattataataccccacctccccccaccatacctcggttcccc
 4126 to 4200

EclHKI

Bsp120I

AhdI

EcoOI

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Eco24I SfcI
 BaniI Bbv16II
 FrioI BbsI DraII BpmI BsgI
 cccaagtgggaagacaacctgtagggcctgcgggtctattcgggaaccaagctggagtgagtggcacaatct
 base pairs
 gggttcaaccttctgttgacatccccggacgccccagataagcccttggttcgacctcacgtcacccgtgtaga
 4201 to 4275
 BpiI EcoO109I GsuI
 09I BpuAI
 ApaI BstSFI

FIG. 12-29

BcoI
 Ama87I
 BcgI
 AvaI
 tggctcactgcaatctcgcctcctgggttcaagcgattctcctgcctcagcctcccggagtgtgtgggattccag
 base pairs
 accgagtgacgttagaggcggaggaccacaagttcgctaaggagcggagtcggagggctcaacaaccctaaggtc
 4276 to 4350

Ec088I
BsoBI

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NSpI	BlpI	MscI
PaeI Mph1103I		MLuNI
Ppu10I EcoT22I	Esp3I	EaeI
gcatacgatgaccaggctcagctaatttttggtagagacggggtttccaccataattggccaggctgggc		
base pairs		
cgtagcgtactggtccgagtcgattaaaaaaacacatctctgccccaaagtgggtataaacgggtccgaccag		
4351 to 4425	BsmBI	CfrI
BbuI Zsp2I CelII		Bali
SphI	Bsp1720I	
NsiI	Bpu1102I	

FIG. 12-30

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FIG. 12-31

BbiII NcoI
 HinII StyI
 AclI AatII EcoT14I
 DraI
 cccttccctgtccttctgtgatttttaaaataactataccagcaggagacgtccagacacagcataggctacctgcc
 base pairs
 gggaaggacaggaagactaaaattttattgatatggtcgctcctcctgcagggtctgtgtcgatccgatggacgg
 4501 to 4575
 Msp17I BssT1I
 BsaHI ErhI
 Hsp92I BspMI

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Eco130I BsrFI PflMI
 DsaI AgeI Bse118I
 BsaWI AccB7I
 atggcccaaccggtgggacatttgagttgcttgccactgtcctctcatgcgttgggtccactcagtagatg
 base pairs
 taccgggttggccaccctgttaactcaacgaaccgtgacaggagagtagcgaaccagggtgagtcattctac
 4576 to 4650
 BssAI Esp1396I
 BstDSI PnaI Van91I
 Bsp19I Cfr10I

FIG. 12-32

EaeI AlwNI
 cctgttgaattgggtacggcgccagcttctgtggaatgtgtgtcaggttaggtgtggaagtccccaggctcccc
 base pairs
 ggacaacttaacccatgcgccgggtcgaagacacaccttacacacagtcaatcccacacctttcaggggtccgagggg
 4651 to 4725

CfrI

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NspI PaeI Mph1103I SexAI
 Ppu10I EcoT22I
 agcaggcagaagtatgcaaaagcatgcatctcaattagtcagcaaccagggtgtggaaaagtccccaggctccccag
 base pairs
 tcgtccgtcttcatacgtttcgtacgtagagttaatcagtcggttggtcccacaccttttcaggggtccgaggggtc
 4726 to 4800

BbuI Zsp2I
 SphI
 NsiI

FIG. 12-33

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NspI
PaeI Mph1103I
Ppu10I EcoT22I
caggcagaagtatgcaaaagcatgcatctcaattagtcagcaaaccatagtcgccgcccctaactccgcccattccccgc
base pairs
gtccgtcttcatacgtttcgtacgtagagttaatcagtcgcttggtatcagggcggggtatgaggggggtagggcg
4801 to 4875

BbuI Zsp2I
SphI
NsiI

NcoI Bsp19I
StyI BstDSI
EcoT14I
ccctaactccgcccagttccgcccattctccgcccattggctgactaatTTTTTTTatttattgcagagggccgagg
base pairs
gggattgagggcgggtcaaggcgggttaagagggcggtaccgactgattaaaaaaaaataaatcgtctccgggtcc
4876 to 4950

BssT1I
ErhI Eco130I
DsaI

FIG. 12-34

SseBI AvrII
 Eco147I BlnI
 StuI BstXI
 BseRI
 BglI
 ccgcctcggcctctgagctattccagaagtagtgaggagccttttttgaggcctaggcttttgcaaaaagctc c
 base pairs
 gccggagccggagactcgataaggcttccatcactcctccgaaaaaacctccggatccgaaaacgttttttcgagg
 4951 to 5025
 SfiI
 AatI StyI
 Pme55I ErhI
 EcoT14I Eco130I
 75/173
 Ama87I
 Eco88I BseRI
 AvaI BsoBI
 SfcI
 ApoI
 tcgaggaactgaaaaaccagaaagtaattccctatagtgagtcgtattaaattcgtaatcatggtcatagctgt
 base pairs
 agtccttgacttttttggtctttcaattaagggatatcactcagcataatttaagcattagtagcagtagtatcgaca
 5026 to 5100
 XhoI BcoI
 Sfr274I
 Paer7I
 BstSFI
 AcsI

FIG. 12-35

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AccBSI

BsrBI

ttcctgtgtgaaattgttatccgctcacaaattccacacatacagagccggaagcataaaagtgtaaagcctggg
 base pairs
 aaggacacactttaacaataggcgagtggttaagggtgtgtgtatgctcggccttcgtatttcacatttcggaccc
 5101 to 5175

BstD102I

AccB1I

BshNI

VspI

PshBI

gtgcctaagtgtgagctaaactcacattaattgcgttgcgctcactgcccgtttccagtcgggaaacctgtcgt
 base pairs
 cacggattactcactcgattgagtgtaattaacgcaacgcgagtgacgggcaagggtcagccctttggacagca
 5176 to 5250

BamI

Eco64I

AsnI

AseI

FIG. 12-36

VspI
 MspA1I
 PvuII PshBI EaeI
 gccagctgcattaatgaatcgGCCCAACGCGGGGAGAGCGGTTTGCgtattggggcgctcttccgcttccctcgc
 base pairs
 cggtcgacgtaattacttagccggttgCGGCCCTCTCCGCAACGCATAAACCCGCGAGAAAGCGAAGGAGCG
 5251 to 5325
 NspBII CfrI
 AsnI
 AseI
 HaeII EarI
 SspI
 Ksp632I
 77/173
 BstMCI AccBSI
 BsaOI BsrBI
 tcaactgactcgctcggtcggtcggtcggtcggtcggtcggtcactcaaaaggcggttaatacgggttat
 base pairs
 agtgactgagcgacgcgagccagcaagccgacgcgctcgccatagtcgagtgagttccgcccattatgcccaata
 5326 to 5400
 Bsh1285I BstD102I
 BsiEI

FIG. 12-37

78/173

NspI

BspLU11I

ccacagaatcaggggataaacgcaggaaagaaacatgtgagcaaaaggccagcaaaaggccaggaaaccgtaaaaagg
base pairs
gggtgtcttagtccccctattgcgtccctttcttgtaacctcggtttccggtcgtttccggtccttggcattttcc
5401 to 5475

AflIII

DrdI

ccgcgttgctggcgtttttccataggctccgccccctgacgagcatcacaaaaatcgacgctcaagtcagaggt
base pairs
ggcgcaacgacccgcaaaaaggatccgaggcgggggactgctcgtagtgttttttagctgcgaggttcagttctcca
5476 to 5550

FIG. 12-38

BsII
 ggcgaaacccgacaggactataaagataccaggcggttccccctggaagctccctcggtcgtcctgttccga
 base pairs
 ccgctttgggctgtcctgataatttctatggtccgcaaaggggaccttcgaggagcacgcgagaggaaggct
 5551 to 5625

BssSI

79/173

BsaWI
 ccctgccgcttacccggatacctgtccgcctttctcccttcgggaagcgtggcgcttctcaatgctcacgctgta
 base pairs
 gggacggcggaatggcctatggacaggcggaagagggaagcccttcgcaccgcgaaagagttacgagtcgcgacat
 5626 to 5700

BstH2I
 Bsp143II

SfcI

HaeII
 BstSFI

FIG. 12-39

BsiHKAI	NspBII
Alw44I	BstMCI
VneI Bbv12I	BsaOI
ggatatcagttcgggtgtaggtcggtcgctccaagctgggctgtgtgcacgaaccccccggttcagcccgaccgct	
base pairs	
ccatagagtcaagccacatccagcaagcgagggttcgacccgacacacacgtgcttgggggggcaagtgcgggctggcgga	
5701 to 5775	
ApaLI	Bsh1285I
AspHI	BsiEI
Alw21I	MspAII
	80/173

BsaWI	AlwNI
gcgccttatccggttaactatcggtcttgagtccaacccggtaagacacgacttatcgccactggcagcagccactg	
base pairs	
cgcggaataggccattgatagcagaactcaggttgggccattctgtgctgaatagcggtgaccgtcggtcggtgac	
5776 to 5850	

FIG. 12-40

81/173

SfiI

gtaacaggattagcagagcgaggatgtaggcgggtgctacagagttcttgaaagtggcctaactacggctaca
base pairs
cattgtcctaatacgtctcgctccatacatccgccacgatgtctcaagaacttcaccaccggattgatgccgatgt
5851 to 5925

BstSFI

Eco57I

ctagaagaacagtgatttggtatctgcgctctgctgaagccaggttaccttcggaataaagagttggtagctcttgat
base pairs
gatcttcttgtcataaaccatagacgcgagacgacttcgggtcaatggaagccttttctcaaccatcgagaacta
5926 to 6000

FIG. 12-41

MflI
 XhoII
 NspBII
 ccggcaaaaccaccgctggtagcgggtgttttttgcaggcagcagattacgcgcagaaaaaaggat
 base pairs
 ggccgtttgttggtggcgaccatcgccacccaaaaaacggtcgctcgaatgcgcgtctttttttccta
 6001 to 6075
 MspAII
 BstYI
 BstX2I

82/173

MflI
 XhoII
 ctcaagaagatccttttgatcttttctacggggtctgacgctcagtggaaacgaaaaactcacgttaagggttttgg
 base pairs
 gattcttcttaggaaactagaaaaagatgccccagactgcgagtcaccttgcttttgagtggcaattccctaaacc
 6076 to 6150
 BstYI
 BstX2I

FIG. 12-42

83/173

RcaI	MflI	MflI	XhoII	DraI	DraI
	XhoII		XhoII		

tcatagagattatcaaaaaaggatccttcacctagatccttttaaatataaaatgaagttttaaatcaatcctaaagta
 base pairs
 agtactctaatagttttccctagaagtgatctaggaaaatttaatttttacttcaaaatttagtagatttcacat
 6151 to 6225
 BspHI BstYI BstYI
 BstX2I BstX2I

	AccB1I
	BshNI

tatatgagtaaacttggtctgacagttaccaatgcttaataatcagtgaggcacctatctcagcgatctgtctatttc
 base pairs
 atatactcaatttgaaccagactgtcaatgggttacgaattagtcactccgtggatagagtcgctagacagataaag
 6226 to 6300
 Bani
 Eco64I

FIG. 12-43

84/173

Fam1105I
 AspEI
 gttcatccatagttgacctgactccccgctgctgttagataactacgatacgggagggttaccatctggccccagtg
 base pairs
 caagtaggtatcaacggactgaggggcagcacatctattgatgctatgccctcccgaatggtagaccgggggtcac
 6301 to 6375
 EclHKI
 AhdI

BsrDI BsaI BssAI BpmI BglI
 Cfr10I
 ctgcaatgataccgcgagaccacgctcacccggctccagatttatcagcaataaacagccagccggaagggccg
 base pairs
 gacgttactatggcgctctgggtgcgagtgggccgaggtctaaatagtcggtatttggtcggtcggccttccccggc
 6376 to 6450
 Eco31I BsrFI Gsui
 Bse118I

FIG. 12-44

VspI
PshBI
agcgagaagtggctcctgcaactttatccgcctccatccagctctattaattgttgccgggaagctagagtaagta
base pairs
tcgcgtcttcaccaggacggttgaaataggcggaggttaggtcagataattaacaacggcccttcgatctcattcat
6451 to 6525

AsnI
AseI

85/173

AviII
FspI
gttcgccagttaatagtttgcgcaacggttggtgccattgctacaggcatcggtggtgtcacgctcgctgttggtta
base pairs
caagcgggtcaattatcaaacgcggttgcaacaacggtaacgatgtccgtagcaccacagtgcgagcagcaaacat
6526 to 6600

BstSFI
SfcI
MslI

Acc16I
Psp1406I
BsrDI

FIG. 12-45

86/173

BsaWI
tggcttcattcagctccggttcccaacgatcaaggcgagttacatgatcccccatgttggtgcaaaaaagcgggta
base pairs
accgaagtaagtcgaggccaagggttgctagttccgctcaatgtactagggggtacaaacacggttttttcgccaat
6601 to 6675

BstMCI
PvuI BsiEI
BsaOI EaeI MslI
gctccttcggtcctccgatcgttgtcagaagtaagttggccgcagtggttatcactcatgggttatggcagcactgc
base pairs
cgaggaagccaggaggtagcaacagtccttcattcaaccggcggtcacaatagtgagtaccaataccgtcgtgacg
6676 to 6750
BspCI CfrI
Bsh1285I
Ple19I

FIG. 12-46

Acc113I
 Eco255I
 ataattcttactgtcatgccatccgtaagatgcttttctgtgactggtgagtactcaaccaagtcatcttgag
 base pairs
 tattaagagaatgacagtagcggtaggcattctacgaaaagacactgaccactcatgagttggttcagtaagactc
 6751 to 6825
 ScaI

87/173

BstMCI BbiII
 BsaOI BcgI BsaHI
 Aatagtgtagcgccgacccgagttgctcttgcccgcggtcaatacgggataataccggccacatagcagaactt
 base pairs
 ttatcacatacgccgctgggtcaacgagaacggccgcgagttatgccctattatggcgcggtgtatcgctctgaa
 6826 to 6900
 Bsh1285I Msp17I
 BsiEI BsaHI
 Hsp92I

FIG. 12-47

88/173

Alw21I	XmnI	MflI	MflI
AspHI	Psp1406I	XhoII	NspBII XhoII
DraI			

taaaagtgcctcatcattggaaaacgttcttcggggcgaaaactctcaaggatcttaccgctgttgagatccagtt
 base pairs
 atttcacgagtagtaaccttttgcagaagccccgcttttgagagttcctagaatggcgacaactctaggtcaa
 6901 to 6975

BsiHKAI	Asp700I	BstYI	MspAII BstYI
Bbv12I		BstX2I	BstX2I

BssSI	Eco57I
Alw44I Bbv12I	
VneI BsiHKAI	

cgatgaaccactcgtgcacccaactgatcttcagcatcttttactttcaccagcgtttctgggtgagcaaaaa
 base pairs
 gctacattgggtgagcacgtgggttgactagaagtcgtagaaaatgaaagtggtcgcaagaccactcgttttt
 6976 to 7050

-ApaLI Alw21I
BsiI
AspHI

FIG. 12-48

EarI
 MslI
 Ksp632I
 caggaaggcaaaatgccgcaaaaaagggaataaggcgacacggaaatgttgaatactcatactcttccttttcc
 base pairs
 gtccttccggttttacggcggtttttcccttattcccgctgtgcctttacaaacttatgagtatgagaaggaaaaag
 7051 to 7125

89/173

SspI
 RcaI
 AccBSI
 BsrBI
 BspHI
 BstD102I
 aatattattgaagcatttatcagggttattgtctcatgagcggatacatatattgaatgtatttagaaaaataaac
 base pairs
 ttataataacttcgtaaatagtcaccaataaacagagtagtcgcctatgtataaaacttacataaatctttttatttg
 7126 to 7200

FIG. 12-49

91/173

BsrFI	
BssAI	NaeI
MroNI	Bse118I
cctttctcgccacgttcgcggtttccccgtcaagctctaaatcgggcatcccttttagggtccgatttagtg	
base pairs	
ggaaagagcgggtgcaagcgccgaaaggcgagttcgagatttagccccgtaggggaaatcccaaggctaataacac	
7351 to 7425	
NgoAIV	
NgomI	
Cfr10I	
AccB1I	
BshNI	BsaAI
ctttacggcacctcgacccccaaaaacttgattagggatggttcacgtagtggcccatcgccctgatagacgg	
base pairs	
gaaatgccggtggagctggggtttttgaactaatcccactaccaagtgcaccccggtagcgggactatctgcc	
7426 to 7500	
BanI	DraIII
Eco64I	

FIG. 12-51

92/173

DrDI

tttttgcgccttgacgttgagtgccacgttctttaatagtggactcttgttccaaactggaacaacactcaacc
base pairs
aaaaagcgggaaactgcaacctcaggtgcaagaaattatcacctgagaacaaggtttgacctgtgtgagttgg
7501 to 7575

ctatctcgggtctattcttttgatttataagggttttgccgattttcggcctatttggttaaaaaatgagctgattt
base pairs
gatagagccagataagaaaaactaaatatccctaaaacggctaaaagccggataaccaattttttactcgactaaa
7576 to 7650

FIG. 12-52

ApoI SspI Psp1406I
 aacaaaatttaacgcgaatttttaacaaaataattaaacggtttacaattt base pairs
 ttgttttttaaatgcttaaaattgttttataatttgcaaatgttataaa 7651 to 7699
 ACSI ACSI

Table by Enzyme Name

Enzyme name	No. cuts	Positions of sites	Recognition sequence
AatI	3	3446 3546 5002	agg/cct <u>More info</u>
AatII	5	451 504 587 773 4550	gacgt/c <u>More info</u>
Acc113I	1	6804	agt/act <u>More info</u>
Acc16I	2	21 6546	tgc/gca <u>More info</u>
Acc65I	3	2264 3434 3998	g/ gtacc <u>More info</u>
AccB1I	8	791 2264 3065 3434 3998 5175 6272 7432	g/ gyrcc <u>More info</u>
AccB7I	6	1445 1482 1775 1796 2644 4587	ccannnn/ntgg <u>More info</u>
AccBSI	4	5126 5367 7168 7332	gagcgg <u>More info</u>
Ac1NI	1	326	a/ ctagt <u>More info</u>
AcSI	8	912 1990 2244 2994 3963 5075 7656 7667	r/ aatty <u>More info</u>
AcYI	6	448 501 584 770 4547 6861	gr/cgyc <u>More info</u>

FIG. 12-53

AflIII	3	2702 3796 5431	a/ crygt	<u>More info</u>
AgeI	1	4584	a/ ccggt	<u>More info</u>
AhdI	2	4150 6324	gacnnn/nngtc	<u>More info</u>
Alw21I	6	894 1576 2330 5749 6910 6995	gwgw/c	<u>More info</u>
Alw44I	2	5745 6991	g/ tgcac	<u>More info</u>
AlwNI	6	1147 1273 1775 3091 4678 5847	cagnnn/ctg	<u>More info</u>
Ama87I	3	4034 4330 5025	c/ ycgrg	<u>More info</u>
AocI	3	1034 1046 3256	cc/ tnagg	<u>More info</u>
Apal	1	4202	gggcc/c	<u>More info</u>
ApalI	2	5745 6991	g/ tgcac	<u>More info</u>
ApoI	8	912 1990 2244 2994 3963 5075	r/ aatty	<u>More info</u>
		7656 7667		
AseI	4	334 5202 5261 6496	at/ taat	<u>More info</u>
AsnI	4	334 5202 5261 6496	at/ taat	<u>More info</u>
Asp700I	5	1107 2481 3506 3906 6923	gaann/nnttc	<u>More info</u>
Asp718I	3	2264 3434 3998	g/ gtacc	<u>More info</u>

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FIG. 12-54

FIG. 12-55

BclI	1	969	t/ gatca	<u>More info</u>
BcoI	3	4034 4330 5025	c/ ycgrg	<u>More info</u>
BglI	5	14 417 538 4956 6444	gcnnnn/nggc	<u>More info</u>
BglII	2	932 3409	a/ gatct	<u>More info</u>
BlnI	2	3109 5003	c/ ctagg	<u>More info</u>
BlpI	3	1200 2337 4366	gc/tnagc	<u>More info</u>
BpiI	2	2512 4216	gaagac	<u>More info</u>
BpmI	10	1015 1279 1772 2781 2842 3022	ctggag	<u>More info</u>
		3892 4097 4259 6414		
Bpu1102I	3	1200 2337 4366	gc/tnagc	<u>More info</u>
Bpu14I	3	1603 1988 2423	tt/cgaa	<u>More info</u>
BpuAI	2	2512 4216	gaagac	<u>More info</u>
Bsa29I	1	939	at/ cgat	<u>More info</u>
BsaAI	3	666 2705 7473	yac/gtr	<u>More info</u>
BsaHI	6	448 501 584 770 4547 6861	gr/cgyc	<u>More info</u>
BsaI	3	3380 4427 6396	ggtctc	<u>More info</u>
BsaMI	3	1886 3631 3936	gaatgc	<u>More info</u>
BsaOI	7	42 424 928 5347 5771 6694 6843	cgry/cg	<u>More info</u>
BsaWI	6	3200 3995 4584 5637 5784 6615	w/ ccggw	<u>More info</u>
BscI	1	939	at/ cgat	<u>More info</u>

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FIG. 12-56

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Bse118I	3	4584 6404 7368	r/ ccggy	<u>More info</u>
Bse21I	3	1034 1046 3256	cc/ ttagg	<u>More info</u>
BseCI	1	939	at/ cgat	<u>More info</u>
BseRI	5	1337 1671 3725 4989 5027	gaggag	<u>More info</u>
BsgI	3	2315 3212 4264	gtgcag	<u>More info</u>
Bsh1285I	7	42 424 928 5347 5771 6694 6843	cgry/cg	<u>More info</u>
BshNI	8	791 2264 3065 3434 3998 5175	g/ gyrcc	<u>More info</u>
		6272 7432		
BsiEI	7	42 424 928 5347 5771 6694 6843	cgry/cg	<u>More info</u>
BsiHKAI	6	894 1576 2330 5749 6910 6995	gwgw/c	<u>More info</u>
BsiI	2	5609 6993	ctcgtg	<u>More info</u>
BsmBI	3	2023 2773 4397	cgtctc	<u>More info</u>
BsmI	3	1886 3631 3936	gaatgc	<u>More info</u>
BsoBI	3	4034 4330 5025	c/ ycgrg	<u>More info</u>
Bsp106I	1	939	at/ cgat	<u>More info</u>
Bsp119I	3	1603 1988 2423	tt/cgaa	<u>More info</u>
Bsp120I	1	4198	g/ ggccc	<u>More info</u>
Bsp1407I	2	270 3471	t/ gtaca	<u>More info</u>
Bsp143II	5	2519 5309 5679 7318 7326	rgcgc/y	<u>More info</u>
Bsp1720I	3	1200 2337 4366	gc/tnagc	<u>More info</u>
Bsp19I	6	686 3324 3424 3600 4574 4910	c/ catgg	<u>More info</u>

FIG. 12-57

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BspCI	2	42 6694	cgat/cg	<u>More info</u>
BspDI	1	939	at/ cgat	<u>More info</u>
BspHI	3	1891 6151 7159	t/ catga	<u>More info</u>
BspLU11I	1	5431	a/ catgt	<u>More info</u>
BspMI	2	1913 4574	acctgc	<u>More info</u>
BspXI	1	939	at/ cgat	<u>More info</u>
BsrBI	4	5126 5367 7168 7332	gagcgg	<u>More info</u>
BsrDI	4	245 2827 6383 6565	gcaatg	<u>More info</u>
BsrFI	3	4584 6404 7368	r/ ccgg	<u>More info</u>
BsrGI	2	270 3471	t/ gtaca	<u>More info</u>
BssAI	3	4584 6404 7368	r/ ccgg	<u>More info</u>
BssSI	2	5609 6993	ctcgtg	<u>More info</u>
BssT1I	13	686 1950 2226 3109 3324 3424 3547 3600 4077 4456 4574 4910 5003	c/ cwwgg	<u>More info</u>
BstBI	3	1603 1988 2423	tt/cgaa	<u>More info</u>
BstD102I	4	5126 5367 7168 7332	gagcgg	<u>More info</u>
BstDSI	7	686 1062 3324 3424 3600 4574 4910	c/ crygg	<u>More info</u>
BstH2I	5	2519 5309 5679 7318 7326	rgcgc/y	<u>More info</u>

FIG. 12-58

DraI	5	3981	4523	6190	6209	6901	ttt/aaa	<u>More info</u>
DraII	3	3291	4198	4225			rg/gnccy	<u>More info</u>
DraIII	1	7476					cacnnn/gtg	<u>More info</u>
DrdI	3	1076	5539	7520			gacnnnn/nngtc	<u>More info</u>
DsaI	7	686	1062	3324	3424	3600 4574	c/ crygg	<u>More info</u>
		4910						
EaeI	10	152	182	236	925	3298 3651 4412	y/ ggccr	<u>More info</u>
		4669	5270	6712				<u>More info</u>
EagI	1	925					c/ ggccg	<u>More info</u>
Eam1104I	5	58	2482	2793	5314	7118	ctcttc	<u>More info</u>
Eam1105I	2	4150	6324				gacnnn/nngtc	<u>More info</u>
EarI	5	58	2482	2793	5314	7118	ctcttc	<u>More info</u>
Ecl1136II	1	892					gag/ ctc	<u>More info</u>
EclHKI	2	4150	6324				gacnnn/nngtc	<u>More info</u>
EclXI	1	925					c/ ggccg	<u>More info</u>
Eco105I	1	666					tac/gta	<u>More info</u>
Eco130I	13	686	1950	2226	3109	3324 3424	c/ cwwgg	<u>More info</u>
		3547	3600	4077	4456	4574 4910		
		5003						
Eco147I	3	3446	3546	5002			agg/cct	<u>More info</u>

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FIG. 12-60

101/173

Eco24I	5	894	1017	1623	3526	4202	grgcy/c	<u>More info</u>
Eco255I	1	6804					agt/act	<u>More info</u>
Eco31I	3	3380	4427	6396			ggtctc	<u>More info</u>
Eco32I	1	952					gat/atc	<u>More info</u>
Eco52I	1	925					c/ggccg	<u>More info</u>
Eco57I	7	1210	2446	2488	3271	3314	ctgaag	<u>More info</u>
		7011						
Eco64I	8	791	2264	3065	3434	3998	g/gyrcc	<u>More info</u>
		6272	7432					
Eco72I	1	2705					cac/gtg	<u>More info</u>
Eco81I	3	1034	1046	3256			cc/tnagg	<u>More info</u>
Eco88I	3	4034	4330	5025			c/ycgrg	<u>More info</u>
EcoICRI	1	892					gag/ctc	<u>More info</u>
EcoNI	4	1259	1338	1684	3723		cctnn/nnnagg	<u>More info</u>
EcoO109I	3	3291	4198	4225			rg/gnccy	<u>More info</u>
EcoRI	3	912	1990	2994			g/aattc	<u>More info</u>
EcoRV	1	952					gat/atc	<u>More info</u>
EcoT14I	13	686	1950	2226	3109	3324	c/cwwgg	<u>More info</u>
		3547	3600	4077	4456	4574		
		5003						
EcoT22I	5	3703	3850	4357	4752	4825	atgca/t	<u>More info</u>

FIG. 12-61

ErhI	13	686	1950	2226	3109	3324	3424	c/ cwwgg	<u>More info</u>
		3547	3600	4077	4456	4574	4910		
		5003							
Esp1396I	6	1445	1482	1775	1796	2644	4587	ccannnn/ntgg	<u>More info</u>
Esp3I	3	2023	2773	4397				cgtctc	<u>More info</u>
FaUNDI	1	560						ca/ tatg	<u>More info</u>
FbaI	1	969						t/ gatca	<u>More info</u>
FriOI	5	894	1017	1623	3526	4202		grgcy/c	<u>More info</u>
FspI	2	21	6546					tgc/gca	<u>More info</u>
GsuI	10	1015	1279	1772	2781	2842	3022	ctggag	<u>More info</u>
		3892	4097	4259	6414				
HaeII	5	2519	5309	5679	7318	7326		rgcgc/y	<u>More info</u>
HinII	6	448	501	584	770	4547	6861	gr/cgyc	<u>More info</u>
HincII	3	311	446	842				gty/rac	<u>More info</u>
HindII	3	311	446	842				gty/rac	<u>More info</u>
HindIII	3	918	1394	2183				a/ agctt	<u>More info</u>
Hsp92I	6	448	501	584	770	4547	6861	gr/cgyc	<u>More info</u>
KpnI	3	2268	3438	4002				ggtac/c	<u>More info</u>
Ksp22I	1	969						t/ gatca	<u>More info</u>
Ksp632I	5	58	2482	2793	5314	7118		ctcttc	<u>More info</u>
LspI	3	1603	1988	2423				tt/cgaa	<u>More info</u>
MfeI	2	1091	3773					c/ aatg	<u>More info</u>
MflI	12	932	2400	2634	3409	3992	4030	r/gatcy	<u>More info</u>

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FIG. 12-62

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MLuNI	5	6072	6083	6169	6181	6949	6966	tgg/cca	<u>More info</u>
Mph1103I	5	184	238	3300	3653	4414		atgca/t	<u>More info</u>
MroNI	1	3703	3850	4357	4752	4825		g/ ccggc	<u>More info</u>
MscI	5	184	238	3300	3653	4414		tgg/cca	<u>More info</u>
MslI	10	691	2094	2703	3323	3489	4047	caynn/nnrtg	<u>More info</u>
Msp17I	6	4094	6576	6735	7094				
MspA1I	7	448	501	584	770	4547	6861	gr/cgyc	<u>More info</u>
MunI	2	71	2341	2731	5255	5773	6018	cmg/ckg	<u>More info</u>
Mva1269I	3	1091	3773					c/ aattg	<u>More info</u>
NaeI	1	1886	3631	3936				gaatgc	<u>More info</u>
NcoI	6	7370						gcc/ggc	<u>More info</u>
NdeI	1	686	3324	3424	3600	4574	4910	c/ catgg	<u>More info</u>
NgoAIV	1	560						ca/ tatg	<u>More info</u>
NgomI	1	7368						g/ ccggc	<u>More info</u>
NotI	1	7368						g/ ccggc	<u>More info</u>
NsiI	5	925						gc/ggccgc	<u>More info</u>
NspBII	7	3703	3850	4357	4752	4825		atgca/t	<u>More info</u>
Nspi	5	71	2341	2731	5255	5773	6018	cmg/ckg	<u>More info</u>
NspV	3	2930	4355	4750	4823	5435		rcatg/y	<u>More info</u>
PaeI	4	1603	1988	2423				tt/cgaa	<u>More info</u>
Paer7I	1	2930	4355	4750	4823			gcatg/c	<u>More info</u>
		5025						c/ tcgag	<u>More info</u>

FIG. 12-63

[illegible]

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FIG. 12-64

SfiI	1	6565	7250	ggcnnnn/nggcc	More info
Sfr274I	1	4956		c/ tgcag	More info
SfuI	3	5025		tt/cgaa	More info
SmaI	1	1603	1988 2423	ccc/ggg	More info
SnaBI	1	4036		tac/gta	More info
SpeI	1	666		a/ ctagt	More info
SphI	4	326		gcatg/c	More info
SseBI	3	2930	4355 4750 4823	agg/cct	More info
SspBI	2	3446	3546 5002	t/ gtaca	More info
SspI	6	270	3471	aat/att	More info
SstI	1	179	226 3571 4164 7128 7681	gagct/c	More info
StuI	3	894		agg/cct	More info
StyI	13	3446	3546 5002	c/ cwwgg	More info
		686	1950 2226 3109 3324 3424		
		3547	3600 4077 4456 4574 4910		
		5003			
Tth111I	1	3674		gacn/nngtc	More info
Van91I	6	1445	1482 1775 1796 2644 4587	ccannnn/ntgg	More info
VneI	2	5745	6991	g/ tgcac	More info
VspI	4	334	5202 5261 6496	at/ taat	More info
XbaI	1	3811		t/ ctaga	More info
XcmI	2	1948	2897	ccannnn/nnntgg	More info

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FIG. 12-65

XhoI	1	5025				c/ tcgag	<u>More info</u>
XhoII	12	932 2400 2634 3409 3992 4030				r/ gatcy	<u>More info</u>
		6072 6083 6169 6181 6949 6966					
XmaI	1	4034				c/ ccggg	<u>More info</u>
XmaIII	1	925				c/ ggccg	<u>More info</u>
XmnI	5	1107 2481 3506 3906 6923				gaann/nnttc	<u>More info</u>
Zsp2I	5	3703 3850 4357 4752 4825				atgca/t	<u>More info</u>

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The following endonucleases were selected but don't cut this sequence:

AccI, AccIII, AfeI, AflII, Aor51HI, AscI, BbeI, BfrI, BsaBI, Bse8I, BseAI, BsePI, Bsh1365I, BsiMI, BsiWI, Bsp13I, Bsp68I, BspEI, BspTI, BsrBRI, BssHII, Bst1107I, Bst98I, BstEII, BstPI, Cfr42I, CpoI, CspI, Eco47III, Eco91I, EcoO65I, Ehel, FseI, HpaI, Kasi, Kpn2I, KspI, Mami, MluI, MroI, MspCI, NarI, NheI, NruI, PacI, Pfl23II, PmeI, PpuMI, PshAI, Psp5II, PspEI, PspLI, PstNHI, RsrII, SacII, SalI, SbfI, Sfr303I, Sgfi, SgrAI, SmlI, SplI, SrfI, Sse8387I, SstII, SunI, SwaI, Vha464I

FIG. 12-66

FIG. 13A
FIG. 13B
FIG. 13C
FIG. 13D
FIG. 13E

ccattcgcattcaggctgcgaactgttggaaggcgatcgggtgcgggcctcttcgtattaccgagctggcgaaaagg
 ggatgtgctgcaaggcgattaaagtgggtaacgcccagggtttccagtcacgacgttgtaaaacgacggcgagtgccaagct
 gatctaataatattggccattagccatattattcattgggtatatagcataaatcaatatattggctattggccattgcatacgttggatcca
 tatcataataatgtacatttatattggctcatgtccaacattaccgccatgttgacattgattattgactagttattaatagtaataatcaattacg
 gggtcattagttcatagccccatatatggagttccggttacataacttacggtaaatggcccgcctggcgaccgccagcgacccc
 ccgcccgttgacgtcaatagtgacgtatgttcccatagtaacgccaatagggactttccattgacgtcaatgggtggtgagtatttacg
 gtaaaactggccacttggcagtagacatcaagtgtatcatatgccaaagtcggccccctattgacgtcaatgacggtaaatggccccgcct
 agcattatgcccagtagacattacgggaggttcctacttggcagtagacatcactacgtattagtcacgtctattaccatgggtgatgcg
 gtttggcagtagtacaccaatggcggtgtagcgggttgactcacggggattccaagtcctccacccttgcacgtcaatggggaght
 tgttttggcaccaaaatcaacgggactttccaaaatgtcgtataaacccccgttgacgcaaatggcggtagcggtgtacg
 gtgggaggtctatatagaagagctcgttttagtaaccgtcagaattcaagcttgcggccgcagatctatcgatctgcaggatatac
 (EcoRV)
 acc

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FIG. 13A

FIG. 13

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ATGCACAGTATGATCAGCTCAGTGGATGTGAAGTCAGAAGTTCCTGTGGCCTGGAGCCCATCTCACCTTTA
GACCTAAGGACAGACCTCAGGATGATGATGCCCGTGGTGACCCCTGTGTCTCGTGAGAAAGCAATTGCAGCAG
GAA'TTACTTCTTATCCAGCAGCAGCAACAATCCAGAAGCAGCTTCTGATAGCAGAGTTTCAGAAACAGCAT
GAGAACTTGACACGCGCAGCACCAAGCTCAGCTCAGGAGCATATCAAGGAACCTTCTAGCCATAAAACAGCAA
CAAGAACTCCTAGAAAAGGAGCAGAAACTGGAGCAGCAGAGGCAAGAACAGGAAGTAGAGAGGCATCGCAGA
GAACAGCAGCTTCCCTCTCAGAGGCAAAAGATAGAGGACGAGAAAGGCGAGTGGCAAGTACAGAAGTAAAG
CAGAAGCTTCAAGAGTTCCTACTGAGTAAATCAGCAACGAAAGACACTCCAACCTAATGGAAAATAATCATTC
GTGAGCCGCCATCCCAAGCTCTGGTACACGGCTGCCACCCACACATCATTTGGATCAAAGCTCTCCACCCCTT
AGTGGAAACATCTCCATCCTACAAGTACACATTAACAGGAGCACAAGATGCAAAGGATGATTTCCCCCTTCGA
AAAACCTGCCTCTGAGCCCAACTTGAAGGTCCGCTCCAGGTTAAACAGAAAGTGGCAGAGAGGAGAAAGCAGC
CCCTTACTCAGGCGGAAGGATGGAAATGTTGTCACTTTCATTCAAGAAAGCGAATGTTTGAGGTGACAGAAATCC
TCAGTCAGTAGCAGTTCTCCAGGCTCTGGTCCCAGTTCACCAAACAATGGCCCAACTGGCCAACTGGAAGTGTACTGAA
AATGAGACTTTCGGTTTGGCCCTACCCCTCATGCCGAGCAAAATGGTTTACAGCAACGCAATCTTAATTCAT
GAAGATTCCATGAACCTTGCTAAGTCTTTATACCTCTCTCTTTGGCCCAACATTACCTTGGGGCTTCCCCGCA
GTGCCATCCAGCTCAATGCTTCGAATTCACCTCAAGAAAAGCAGAAAGTGTGAGACGACGCTTAGGCAA
GGTGTTCCTCTGCTGGCAGTATGGAGGCAGCATCCCGGCATCTTCCAGCCACCCCTCATGTACTTTAGAG
GGAAAGCCACCAACAGCAGCCACAGGCTCTCTGCAGCATTTATTTAATGAAAAGAACAAATGCCACAGCAA
AAGCTTCTTGTAAGTGTGGAGTTCCTTACATCCTCAGTCTCCCTTGGCAACAAAAGAGAGAAATTTACCT
GGCATTAGAGTACCCACAAAATTGCCCGCTCACAGACCCCTGAACCCAGTCTGCACCTTTTGCCTCAG
AGCACGTTGGCTCAGCTGGTCAATTCAACAGCAACACCCAGCAATTTCTTGAGAAAGCAGAAAGCAATACCAGCAG
CAGATCCACATGAACAACTGCTTTCGAAATCTATTGAACAACTGAAGCAACCCAGGAGTCACTTGGAGAA
GCAGAGGAAGAGCTTCAGGGGACCCAGGCGATGCAGGAAGACAGAGCGCCCTCTTAGTGGCAACAGCACTAGG
AGCGACAGCAGTGTGTGTGGATGACACACTGGGACAAAGTTGGGGCTGTGAAGGTCAAGGAGGAACCCAGTG
GACAGTGAAGATGCTCAGATCCAGGAAATGGAAATCTGGGGAGCAGGCTGCTTTTATGCAACAGCCTTTTC

FIG. 13B

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CTGGAACCCACGCACACGTCGCTCTCTGTGCGCCAAAGCTCCGCTGGCTGCGGTTGGCATGGATGGATTA
GAGAAACACCGTCTCGTCTCCAGGACTCACTCTTCCCTGCTGCTCTGTGTTTTTACCTCACCCAGCAATGGAC
CGCCCTCCAGCCTGGCTCTGCAACTGGAATTGCCCTATGACCCCTTGATGCTGAAACACCAAGTCGTTGT
GGCAATTCCACCAACCCCTGAGCATGCTGGACGAATACAGAGTATCTGGTCACGACTGCAAGAAACTGGG
CTGCTAAATAAATGTGAGCGAATTCAAGGTCGAAAGCCAGCCTGGAGGAAATACAGCTTGTTCATTCTGAA
CATCACTCACTGTTGTATGGCACCAACCCCTGGACGGACAGAAAGCTGGACCCAGGATACTCCTAGGTGAT
GACTCTCAAAGTTTTTTTCTCATTAACCTTGTGGTGGACTTGGGGTGGACAGTGACACCATTTGGAATGAG
CTACACTCGTCCGGTGTGCACGCAATGGCTGTTGGCTGTGTCAATCGAGCTGGCTTCCAAAGTGGCCTCAGGA
GAGCTGAAGAAATGGGTTTGCTGTTGTGAGGCCCCCTGGCCATCACGCTGAAGAAATCCACAGCCATGGGGTTC
TGCTTTTTTAATTCAGTTGCAATTACCGCCAAATACTTGAGAGACCAACTAAATATAAGCAAGATATTGATT
GTAGATCTGGATGTTCAACCATGGAAACGGTACCCAGCAGGCTTTTATGCTGACCCAGCATCCTGTACATT
TCACTCCATCGCTATGATGAAGGGAACTTTTTCCCTGGCAGTGGAGCCCCAAATGAGGTTTCGGTTTATTCT
TTAGAGCCCCACTTTTATTGTATCTTTCAGGTAATTGCATTGCA

FIG. 13C

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(BamHI)ggatccgggtaccagattacaaggacgacgatgacaaagtagatcccgggtggcatcccctgtgaccccctcccagtg
 cctctctggcccttggaagtggccactccagtgccaccagcctgtctctaataaaattaaagtgtgcatcattttgtctgactagtgctc
 ctctataataattatggggaggggggtggtatgagcaaggggcccaagtgggaaagacaacctgtagggccctggcgggggtc
 tattcgggaaaccaagctggagtgagtgacacaatttgggtcactgcaatctccgctcctctgggttcaagcgattctcctggcctc
 agcctcccaggtgttgggattccaggcatgcatgaccaggctcagctaatttttttttttggtagagacgggggttcaccacatttg
 gccaggctggctccaaactcctaattctcagtgatctacccacctggcctcccaattgctgggtattacaggcgtgaaaccactg
 tcccctccctgtctcttctgattttaaaataactataccagcaggagggacgtccagacacacagcatagggctacctggccatggccccaac
 cgggtgggacatttgaggtgcttggcactgtctctctcatgctggtgggtccactcagtagatgacctgttgaattgggtacggcggc
 cagcttctgtggaatgtgtcagttaggggtgtgaaagtccccagggtccccagggtccccagggtcagaaagtatgcaaaagcatgcatctca
 attagtacagcaaccagggtgtgaaagtccccagggtccccagggtcagaaagtatgcaaaagcatgcatctcaattagtcagca
 accatagtccccctaaactcggcccatccccctaaactcggccagttccgcccattctcggcccattggtgctgactaattttt
 ttatttatgcagaggccggaggccgctcggcctctgagctattccagaaagtatgtagggagggcttttttggaggccctagggcttttgc
 aaaaaagctctcggaggaaactgaaaaaacagaaaagttaattccctatagtgagctgtattaaattcgtaatcatggtcatagctgtttc
 ctgtgtgaaattgttatccgtcacaaattccacacaacatacagagccggaaagcatataaagtgtaaagccctgggggtgccataatgagtg
 gagctaaactcacattaatgtcgtcactgccccgctttccagtcggggaaacctgtcgtgccagctgcaattaatgaatcggccc
 aacggcggcggggagaggcgggttgcgtattggggcgtctctccgctcctcactgactgctgctggcgtcggctcgggtcggctgctgg
 gcgagcgggtatcagctcactcaaaaggcggtaatacgggttatccacagaatacagggggataacgcagggaaagaaacatgtgagca
 aaaaggccagcaaaaaggccagaaaccgtataaaaggccggtgtggtgttttccataggtctcggccccctgacgagcatca
 caaaaatcgacgctcaagtcagaggtggcgaaacccgacaggactataaagataccaggcggtttccccctggaaagctcccctcg
 tgcgctctctctgttccgacctgacctacccggtaccccttctcctcctgggaaagcgtggcgctttctcaatgctcac
 gctgtaggtatctcagttcgggtgtaggtcgttctgctccaaagctgggctgtgtgacgaacccccctgttcagccccgacctggcgc
 ctatccggtaactatcgtcttggagtgccaacccgggtaaagacacgactatcggccactggcagcagccactgggtaaacagsgattagc
 agagcggaggtatgtaggcgggtgtctacagaggttctgaaagtgggtggcctaactacgggtctacactagaaagaaacagtatttgggtatct
 gcgctctgtcgtgaagccagtttaaccttccggaaaaagagttgtagtctcttgcgtccggaacaaacaccgctggtgtagcggtgggttt

FIG. 13D

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tttgttgcaagcagattacggcagaaaaaaggatctcaagaagatcccttgatctttttacggsgtctgacgctcagtg
 gaacgaaaaactcacgftaaaggatttggtcatgagattatcaaaaaaggatcttccacctagatccttttaataaaaaatgaagtttta
 aatcaatctaaagtatataatgagtaaaacttggtctgacagttaccaatgcttaatacagtgagcaccctatctcagcgatcgtctctatttc
 gttcatccatagttgctgactcccgtcgtgtagataactacgatacgggagggccttaccatctggccccagtgctgcaatgata
 ccgcgagacccacgctcaccggctccagatttatcagcaataaaacagccagccggaaaggccgagcgcagaagtggctcct
 gcaactttatccggcctccatccagtcatttaattgttggcggaaagctagagtaagtagttccgcaagttaatgtttgcgaacgttgt
 tgccattgctacagggcatcgtggtgtcagcgtcgtcgtttgggtatggcttcaatcagctccgggttcccaacgatcaaggcggaggttac
 atgatcccccatgtgtgcaaaaaagcggtagtctcttcggtcctcgatcgttgcagaagtaaagttggccgcaagtgttatcact
 catggttatggcagcactgcataattcttactgtcatgccatccgtaagatgcttttctgtgactgggtgagtactcaaccaagtcatt
 ctgagaataagtgtatggcggaccgagttgctcttggccggcgtcaatacgggataataaccggccacacatagcagaactttaaaa
 gtgctcatcattggaaaacgttcttcggggcgaaaactctcaaggatcttaccggctgtgagcaaaaacaggaaagcgaataatgcccga
 gcacccaactgatcttcagcatcttttactttaccaggcgtttctgggtgagcaaaaacaggaaagcgaataatgcccgaataatgcccga
 gaataaggcgacacggaaatgttgaatactcatactcttcttcaataattattgaagcattatcagggttattgtctcattgagcgg
 gatacatatttgaatgtatttagaaaaataaacaataagggttcggcgacatttccccgaaaaagtggccacctgacggccccgtgt
 agcggcgcaataagcggcggtgtgtgtgtacggcgagcgtgacccgtacacttgccagcggcccttagcggccccgctccttt
 cgctttctcccttctcgcacgttcggcggttccccggtcaagctctaaatcggggcatcccttaggggttcggatttagtgc
 tttagggcacctcgacccccaaaaaacttgattagggtgtggttcacgtagtgggccatcgccctgatagacgggttttcggcccttt
 gacgttggagtgccacgttctttaatagtgactcttggtccaaactggaaacaacactcaacccctatctcgggtctattcttttgattataa
 gggatttggcgatttcggcctattggttaaaaaaatgagctgatttaacaaaatttaacggcgaattttaacaaaataattaaacgttttac
 aattt

FIG. 13E

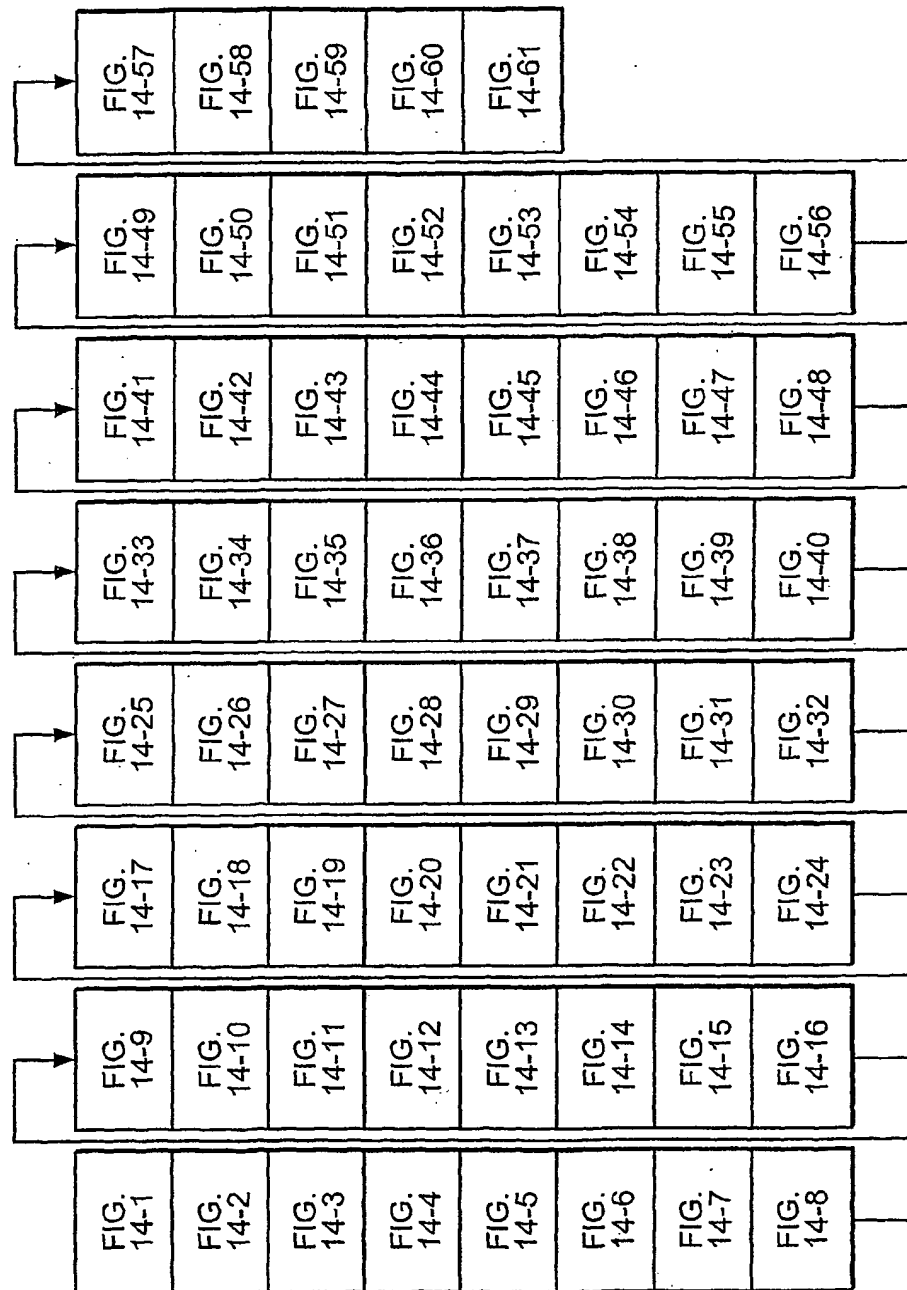


FIG. 14

pFLAG-CMV-5b-HDAC9a

7303 base pairs

Graphic map | Table by enzyme name

BstMCI	
AviII	PvuI BsiEI
BglI FspI	BsaOI
cccatcggccattcaggctgcgcaactgttggaaggcgcatcggtcgggcctcttcgctattaccgagctgg	EamI
base pairs	Eam1104I
gggtaagcggtaagtccgacgcgttgacaacccttcccgctagccacgccccggagagcgataatgcggtcgacc	PvuII
1 to 75	113/173
Acc16I	BspCI
	Bsh1285I
	Ple19I
	Ksp632I
	NspBII

FIG. 14-1

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cgaaggaggatgtgtgcaaggcgattagttgggtaacgccccagggtttcccagtcacgacgttgtaaaacg
base pairs
gctttccccctacacgacgttcgctaattcaaccattgcgggtcccaaaagggtcagtgctgcaacattttgc
76 to 150

MscI
CfrI

SspI MluNI

EaeI

acggccagtgccaagctgatctaataatcaatatttggccattagccatattattcattgggtatatagcataaatcaa
base pairs
tgccgggtcacgggttcgactagattagttataaacccggtaatcgggtataataaagtaaccaatataatcgatttagtt
151 to 225

EaeI
Bali

CfrI

FIG. 14-2

HinII
AcyI
HincII

BstMCI
BglI BsaOI

tatggagtccgcgttacataacttacggtaaatggcccgctggcgaccgcccagcgaccccccggttgacg
base pairs
atacctcaaggcgcaatgtattgaatgccattttaccggcgggaccgctggcggtcgctggggcggggcaactgc
376 to 450

HindII
Hsp92I
Msp17I

Bsh1285I
BsiEI

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BsaHI
AatII
BbiII

BbiII
HinII
AcyI AatII

tcaatagtgacgtatgttcccatagtaacgccaataggactttccattgacgtcaatgggtggagtatttacgg
base pairs
agttatcactgcatacaagggtatcattgcggttatccctgaaaggtaactgcagttaccacacctcataaatgcc
451 to 525

Msp17I
BsaHI
Hsp92I

FIG. 14-4

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<p>BglI</p> <p>taaactgcccaacttggcagtagcatcaagtgtagtgcataatgccaagtcgccccctattgacgtcaatgacggtaaa base pairs</p> <p>atttgacgggtgaaccgtcatgtagttcacatagtagtgcaggttcaggcgggggataactgcagttactgccattt 526 to 600</p>	<p>BbiII</p> <p>HinII</p> <p>NdeI</p> <p>Acyl AatII</p>	<p>FauNDI</p> <p>Msp17I</p> <p>BsaHI</p> <p>Hsp92I</p>	<p>BstSNI</p> <p>SnaBI</p> <p>BsaAI</p> <p>Eco105I</p>
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601 to 675

FIG. 14-5

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NcoI Bsp19I
 StyI BstDSI
 EcoT14I
 atcgctattaccatggatgcggttttggcagtaacccaatggcgtagcggtttgactcacggggattt
 base pairs
 tagcgataatggtaccactacgccaaaacggtcatgtgttaccgcacctatcgccaaactgagtgtccctaaa
 676 to 750
 BssT1I
 ErhI Eco130I
 DsaI MslI
 BbiII
 Hin1I
 AccB1I
 AclI AatII
 BshNI
 ccaagtctccaccatcgacgtcaatgggagttgttttggcaccaaaatcaacgggactttccaaaatgtcgt
 base pairs
 ggttcagaggtgggtaactgcagttaccctcaaaacacccgtggttttagttgccctgaaaggtttacagca
 751 to 825
 Msp17I
 BsaHI
 Hsp92I
 BanI
 Eco64I

FIG. 14-6

HincII
 Eco24I
 EcoICRI
 aataaccccccccggttgacgcaaatgggcggtaggcgtgtacggtgggaggtctatataagca gagctcgttta
 base pairs
 ttattggggcgggggaactgcgtttaccgcccatccgcacatgccaccctccagatatattcgt ctcgagcaaat
 826 to 900
 HindII
 Ecl136II
 Bbv12I
 AspHI
 Psp124BI

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SacI
 FrioI
 SstI
 BanII
 BsiHKAI
 AcsI
 ApoI
 BsiHKAI
 BclI
 Ksp22I
 gtgaaccggtcagaattcaagcttgccgagatctatcgatctgcaggatatcaccatgcacagtatgatcag
 base pairs
 cacttggcagtccttaagttcgaacggcggtctagatagctagacgtcctatagtggtacgtgtcactactagtc
 901 to 975
 EcoRI
 FbaI
 CfrI
 NotI
 Alw21I
 BstSFI
 Bsu15I
 EcoRV
 Bsp106I
 ClaI

FIG. 14-7

ctcagtggtgaagtcagaagttcctgtgggcctggagcccatctcacctttagacctaaggacacctcag	FrIOI	CvnI	CvnI
base pairs	Eco24I	AocI	AocI
gagtcacctacacttcagttctcaaggacacccggacctcgggtagagtggaatctggattcctgtctggagtc	BpmI	Bsu36I	Bsu36I
976 to 1050			
	GsuI	Eco8I	Eco8I
	BanII	Bse2I	Bse2I

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gatgatggtggcccggtggaccctgttgcgtgagaagcaattgcagcaggaattacttcttattccagcagca	DsaI	DrdI	MfeI	Asp700I
base pairs				
ctactactacgggacccacctgggacacacaggcactcttcggttaacgctgccttaataagaagaataggctcgt				
1051 to 1125	BstDSI	MunI	XmnI	

FIG. 14-8

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AlwNI
gcaacaaatccagaagcagcttctgatagcagagtttcagaaacagcatgagaacttgacacggcagcaccaggc
base pairs
cgttggttaggtcttcgtcgaagactatcgtctcaaagtctttgtcgactcttgaaactgtgccgtcgtggtccg
1126 to 1200

BlpI
CelII Eco57I
tcagcttcaggagcatatcaaggaaacttctagccataaaaacagcaacaagaactcctagaaaaggagcagaact
base pairs
agtcgaagtcctcgtatagttccttgaagatcggatatcttgctggttcttgaggatctttcctcgtcttga
1201 to 1275
Bsp1720I
Bpu1102I

FIG. 14-9

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BpmI
BseRI
ggagcagcagaggcaagaacagggaagtagagaggcatcgagagaaacagcagcttcctcctctcagagggcaaga
base pairs
cctcgtcgtctccgttcttgttccttcattctctccgtagcgtctcttgcgaaggagagagtcctccgtttct
1276 to 1350
GsuI
EcoNI

HindIII
tagaggacgagaaagggcagtggaagtagacagaagtaaacag agcttcaagagttcctactgagtaaatcagc
base pairs
atctcctgctcttcccgtaaccgttcatttcgtc ttcgaagttctcaaggatgactcatttagtcg
1351 to 1425

FIG. 14-10

123/173

Van91I	Van91I
AccB7I	AccB7I
aacgaaagacactccaactaatggaaaaaatcattccgtgagccgccatcccaagctctggtacacggctgcccc	
base pairs	
ttgctttctgtgaggttgattaccttttttagtaaggcactcggcggtagggttcgagaccatgtgccgacgggt	
1426 to 1500	
Esp1396I	Esp1396I
PflMI	PflMI
ccacacatcattggatcaaagctctccacccttagtggaacatctccatccataagtagacacattaccaggagc	
base pairs	
ggtgtgtagtaacctagtttcgagaggtggggaatcaccttgtagaggtaggatgttcattgtgtaatggtcctcg	
1501 to 1575	

FIG. 14-11

124/173

Alw21I	BstBI	
AspHI	Bpu14I	FriOI
	Csp45I	Eco24I
acaagatgcaaaaggatgatttcccccttcgaaaaactgcctctgagcccaacttgaaggcggtccagggttaaa		
base pairs		
tgttctacgttttccctactaaaggggaagctttttgacggagactcgggttgaacttccacgccagggtccaattt		
1576 to 1650		
BsiHKA I	SfuI Bsp119I	BanII
Bbv12I	NspV	
	LspI	

	BseRI	EcoNI
acagaaaagtggcagagaggagaagcagcccttactcaggcggaaggatggaaatgttgcatttcaagaa		
base pairs		
tgtctttcaccggtctctccttctcgtcggggaatgagtcggccttcctacctttacaacagtgaaagtaagtctt		
1651 to 1725		

FIG. 14-12

Van91I
 AccB7I
 BpmI PflMI
 Van91I
 AccB7I
 gcgaatgtttgaggtgacagaatcctcagtcagtagcagttctccaggctctggtcccagttcaccaacaatgg
 base pairs
 cgcttacaactccactgtctttaggagtcagtcagtcggtcaagaggtccgagaccagggtcaagtggtttgttacc
 1726 to 1800
 GsuI
 Esp1396I
 PflMI
 125/173
 AlwNI
 Esp1396I

gccaaactggaagtgttactgaaaatgagacttcggttttgccccctaccctcatgccgagcaaatggttcaca
 base pairs
 cggttgaccttcacaatgacttttactctgaagccaaaacgggggatggggagtagcggttcggtttaccacaagtgt
 1801 to 1875

FIG. 14-13

BsaMI
Mva1269I
BspMI
XcmI
gcaacgcattcttaattcatgaagattccatgaacctgctaagtccttataacctctccttcttggcccaacattac
base pairs
cgttgcgtaagattaagtacttctaaggtagtgacgattcgagaaatagggagaggaagaaacgggttgtaatg
1876 to 1950

BsmI RcaI
BspHI

ErhI
BstBI AcsI
BspT1I
Bpu14I
Csp45I
Esp3I
126/173

cttggggcttcccgcagtgccatcccagctcaatgctc gaattcactcaaaagcagaagtgtagagcgca
base pairs
gaaccccgaaagggcgtcacggtagggtaggttacgaag ctttaagttaggtttcttcttcacactctgcgt
1951 to 2025

EcoT14I
SfuI Bsp119I
BsmBI
StyI
NspV ApoI
Eco130I
LspI EcoRI

FIG. 14-14

127/173

gacgcttaggcaagggtgttcctctgcctgggcagtatggaggcagcatcccgcatcttccagccaccctcatgt
base pairs MslI
ctgcgaatccggttccacaaggagacggaccggtcatcacctccgtcgtaggccgtagaagggtcggtgggagtaca
2026 to 2100

taçtttagagggaagccaccaccaacagcagccaccagggtctc ctgcagcatttattattgaaagaacaaatgcg
base pairs PstI
atgaaatctcccttccggtgggtgtcgtcgtcggtggtccgagag gacgtcgtataataaacttcttgtttacgc
2101 to 2175 SfiI

BstSFI

FIG. 14-15

128/173

<p>HindIII</p> <p>acagcaaaagcttctttagctggtgagttcccttacatccctcagttcccttggcaacaaagagagaatttc base pairs tgtcgttttcgaagaacatcgaccacctcaagggaatgtaggagtcagaggggaaccgttggtttctctcttaaag 2176 to 2250</p>	<p>Eco130I</p> <p>StyI</p> <p>EcoT14I</p> <p>ApoI</p>
<p>Asp718I</p> <p>Acc65I</p> <p>BshNI</p> <p>acctggcattagaggtaccacacaaattgccccgtcacagacccctgaaccgaaccagtcctgcaccttgccctca base pairs tggaccgtaatctccatgggtgtttaacggggcagtgctctggggacttggcttgggtcagacgtggaacggaggt 2251 to 2325</p>	<p>BstTlI</p> <p>ErhI</p> <p>AcSI</p> <p>BsgI</p>
<p>BanI</p> <p>KpnI</p> <p>ACCB1I</p> <p>ECO64I</p>	

FIG. 14-16

129/173

Bpu1102I
 Alw21I Bsp1720I
 AspHI CelII
 gagcacgttggctcagctggtcattcaacagcaacaccagcaattcttggagaagcagaagaataaccagcagca
 base pairs
 ctcggtgaaccgagtcgaccagtaagttgtcgttggtcggttaagaacacctcttcgtcttcggttatgggtcggtcgt
 2326 to 2400
 BsiHKAI PvuII
 Bbv12I B1pI MspAI
 NspBII
 BstBI
 Bpu14I
 Csp45I Eco57I
 gatccacatgaacaaactgcttttcgaaatctattgaacaaactgaagcaaccaggcagtcaccttgaggaaagcaga
 base pairs
 ctagggtgacttgttgacgaaagctttagataaacttggtgacttcggttggtccggtcagtggaactccttcgtct
 2401 to 2475
 BstYI
 BstX2I
 SfuI Bsp119I
 NspV
 LspI

FIG. 14-17

130/173

EarI
Eam1104I
Asp700I
ggaagagcttcaggggaccaggcgatgcaggaagacagagcgccctctctagtggaacagcactaggagcgacag
base pairs
ccttctcgaagtcctccctgggtccgctacgtccttctgtctcgcgggagatcacccgttgctcgtgatccctcgctgtc
2476 to 2550
XmnI Eco57I
Ksp632I
SapI
Bbv16II
BbsI Bsp143II
BpiI HaeII
BpuAI BstH2I

BcgI
cagtgtgtgtggatgacacactgggacaagtggggctgtgaagggtcaaggaggaaaccagtggaacagtgtgatga
base pairs
gtcacgaacacacactactgtgtgacctgttcaacccccgacacttccagttcctccttggtcacctgtcactact
2551 to 2625

FIG. 14-18

MflI Van91I
XhoII AccB7I
agatgctcagatccaggaaatggaatctggggagcaggctgttttatgcaacagcctttcctggaacccacgca
base pairs
tctacgagtcaggtcctttaccttagacccctcgtccgacgaaatacgttgtcggaaggaccttgggtgcgt
2626 to 2700
BstYI Esp1396I
BstX2I PflMI

131/173

PmaCI
PmlI
AflIII NspBII
cacacgtgcgctctctgtgcgccaagctccgctggctgcggttggcatggatgagaaacacgcgtctcgt
base pairs
gtgtgcacgcgagagacacgcggttcgaggcgaccgacgccaacgtacctaatactcttggcagagca
2701 to 2775
MslI Eco72I MspAII
BsaAI BsmBI
BbrPI

FIG. 14-19

132/173

EaRI	BpmI	BsrDI	BpmI
Eam1104I			
ctccaggactcactcttcccctgctgcctctgttttacctcaccagcaatggaccgccccctccagcctggctc			
base pairs			
gaggtcctgagtgagaaggggacgacggagacaaaaatggagtgggtcggttacctggcgggggaggtcggaccgag			
2776 to 2850			
GsuI	Ksp632I		GsuI

	XcmI
tgcaactggaattgcctatgaccccttgatgctgaacaccagtgcggtttgtggcaattccaccaccaccctga	
base pairs	
acgttgacccttaacggatactggggaactacgactttgtggtcacgcaaacacacggttaagggtgggtgggact	
2851 to 2925	

FIG. 14-20

133/173

SphI
BbuI
gcattgctggacggaatacacagagtattctggtcacgactgcaagaaactgggctgctaaaaaatgtgagc gaattca
base pairs
cgtacgacctgcttatgtctcatagaccagtgtgacgttctttgacccgacgatttattttacactcg cttaagt
2926 to 3000
PaeI
NspI
AcsI
ApoI
EcoRI

BpmI
aggtcgaaaagccagcctggaggaaatacacagcttgttcattctgaacatcactcactgttgtatggcaccaccc
base pairs
tccagcttttcggtcggacctcctttatgtcgaacaagtaagacttgtagtgtgacaacataccgtggttggg
3001 to 3075
GsuI
AccB1I
BshNI
BamI
Eco64I

FIG. 14-21

ErhI
StyI Eco130I
EcoT14I
AlwNI
BstXI
cctggacggacagaagctggacccaggatactcctaggatgactctcaaaagtttttctctcattaccttg
base pairs
ggacctgcctgtcttcgacctgggggtcctatgaggatccactactgagagttttcaaaaaaggagtaatggaac
3076 to 3150

BsStII
AvrII
BlnI

BsaWI BsgI
 ttggtggacttgggtggacagtgacaccatttgaatgagctacactcgtccggtgctgcacgcacatggctgttgg
 base pairs
 accacctgaacccacactgtcactgtggtaaaccttactcgatgtgagcaggccacgacgtgcgtaccgacaacc
 3151 to 3225

FIG. 14-22

Cvnl	CfrI
AocI	DraII EaeI
Bsu36I	Eco57I
ctgtgtcatcgagctggcttccaaagtggcctcaggagagctgaagaatgggtttgctgtgtgagggccccctgg	
base pairs	
gacacagtagctcgaccgaaggtttcacggagtcctctcgacttcttacccaaacgacaacactccgggggggacc	
3226 to 3300	
Eco81I	Eco0109I
Bse21I	

135/173

MscI	ErhI Eco130I
	BssT1I BstXI
	Eco57I MslI DsaI
ccatcacgctgaagaatccacagccatgggggtctgtcttttttaattcagttgcaattaccgccaatacttgag	
base pairs	
ggtagtgcgacttcttaggtgtcggtaccccccaagacgaaaaaattaagtcaacgttaatggcggttttatgaactc	
3301 to 3375	
MluNI	EcoT14I
BalI	StyI BstDSI
	NcoI Bsp19I

FIG. 14-23

BstX2I NcoI Bsp19I Asp718I SseBI
 BstYI StyI BstDSI AccB1I
 XhoII EcoT14I BshNI StuI
 BsaI
 agaccaactaaatataagcaagatatattgattgtagatctggatgttcaccatggaaacgggtaccaggcagcctt
 base pairs
 tctgggtgatttataattcgttctataactaacatctagacctacaagtggtaacctttgccatgggtcgtccggaa
 3376 to 3450
 Eco31I
 BglII Bst1I Bani KpnI AatI
 MflI ErhI Eco130I Eco64I Pme55I
 DsaI Acc65I
 136/173
 SspBI
 Bsp1407I MslI Asp700I
 ttatgctgacccagcatcctgtacatttcactccatcgctatgatgaagggaactttttccctggcagtgaggc
 base pairs
 aatacgactgggtcgtaggacatgtaaagtgaggtagcgatactacttcccttgaaaaaggacccgtcacctcg
 3451 to 3525
 BsrGI XmnI

FIG. 14-24

FriOI	FriOI	BstYI
Eco24I	Eco24I	XhoII
cccaaatgaggttcggtttatttcttttagagccccactttttatttgatatctttcaggtaattgcattgca ggatc		BsrDI
base pairs		
gggtttactccaagccaaataaaagaatctcggggtgaaaataaacatagaaaagtcattaaacgtaacgt cctag		
3526 to 3600		
BanII	BanII	BamHI
		BstI
		MflI

Acc65I	AvaI BcoI	137/173
BanI Eco64I	MflI Eco88I PspALI	
BstX2I Asp718I	XhoII Cfr9I SmaI MslI	
cgtaccagattacaaggacgacgatgacaagtagat cccgggtggcatccctgtgacccctccccagtgccctct		
base pairs		
gccatgggtctaattgttcctgctgctactgttcatcta gggccaccgtagggacactggggagggtcacgggaga		
3601 to 3675		
BshNI	BstYI Ama87I	
BsaWI KpnI	BstX2I BsoBI	
AccB1I	XmaI PspAI	

FIG. 14-25

Eco130I
 StyI
 EcoT14I
 GsuI
 MslI
 cctggccttggaagtggccactccagtgccaccagccttgctcctaataaaattaagttgcatcattttgtctga
 base pairs
 ggac'cggaaccttcaacggtgaggtcacgggtggcggaacaggattattttaattcaacgtagtaaaacagact
 3676 to 3750
 BssT1I
 BpmI
 ErhI
 Eco24I
 138/173
 SfcI
 Bbv16II
 DraII BanII
 PspOMI FrlOI
 SspI
 Eam1105I
 AspEI
 ctaggtgtcctctataataattatgggtggaggggtggtatggagcaagggggcccaagttgggaagacaacct
 base pairs
 gatccacaggagatatataataacccacacctccccaccataacctgttccccgggttcaaaccttctgttggga
 3751 to 3825
 EclHKI
 AhdI
 Bsp120I
 EcoO109I
 BpiI
 BpuAI
 ApaI
 BstSFI

FIG. 14-26

DraII
 gtagggcctgcgggtctattcgggaaccaagctggagtgcgagtgggcacaaatcttgggtcactgcaatctccgcc
 base pairs
 catcccgagcggccagataagcccttggttcgacctcacgtcacccgtgttagaaccgagtgacgttagaggcgg
 3826 to 3900
 Eco0109I
 GsuI
 139/173
 BcoI
 Ama87I
 BcgI
 AvaI
 NspI
 PaeI
 Ppu10I
 EcoT22I
 BlnI
 Mph1103I
 EcoT22I
 tcctgggttcaagcgattctcctgcctcagcctcccaggttggttgggattccaggcatgaccagggtcagc
 base pairs
 aggacccaagttcgctaagaggacggagtcggagggtcaacaaccctaagggtccgtactggtccgagtcg
 3901 to 3975
 Eco88I
 BsoBI
 BbuI
 Zsp2I
 CelII
 SphI
 Bsp172
 NsiI
 Bpu1I

FIG. 14-27

140/173

	MscI		
	MluNI		BsaI
	Esp3I	EaeI	
taatttttgggttagagacgggtttcaccataattggccagggtgtctccaactcctaattctcagggtg			
base pairs			
attaaaaaaccatctctgtgccccaaagtgtataaacgggtccgaccagaggttgaggattagagttccac			
3976 to 4050	BsmBI	CfrI	Eco31I
		BalI	
0I			
02I			
	Eco130I		
	StyI		
	EcoT14I	BstXI	
atctaccacacttggcctcccaaatgtgctgggttacaggcgtgaaccactgctcccttccctgtccttctgatt			
base pairs			
tagatgggtggaaccggagggtttaacgaccctaattgtccgcaacttggtgacgaggggaaggacaggaagactaa			
4051 to 4125	BssT1I		
	ErhI		

FIG. 14-28

Msp17I Bst1I BsaI Esp1396I
BsaHI ErhI BstDSI PinAI Van91I
Hsp92I BspMI Bsp19I Cfr10I

ttgagttgcttgcttgccactgtcctctcatgcgttgggtccactcagtagatgcctgttgaaattgggtacgcgg	EaeI
base pairs	
aaactcaacgaacggtgacaggagagtagcgaaccagggtgagtcattctacggacaactaaccatgcgcc	
4201 to 4275	CfrI

FIG. 14-29

142/173

AlwNI
ccagcttctgtggaatgtgtgcagttaggggtgtggaagtccccagggtccccagcaggcagaagtatgcaaaag
base pairs
ggtcgaagacacaccttacacacagtcgaatccccacacctttcaggggtccgaggggtcgccgtcttcatacgttttc
4276 to 4350

NspI
PaeI Mph1103I
Ppu10I EcoT22I SexAI
catgcatctcaattagtcagcaaccagggtgtggaagtccccagggtccccagcaggcagaagtatgcaaaagca
base pairs
gtacgtagaggttaatcagtcggttggtccacaccttttcaggggtccgaggggtcgccgtcttcatacgttttcgt
4351 to 4425
BbuI Zsp2I
SphI
NsiI

FIG. 14-30

143/173

NspI
 PaeI Mph1103I
 Ppu10I EcoT22I
 tgcatctcaattagtcagcaaccatagtcgcccccctaactccgcccatactccgcccagttccg
 base pairs
 acgtagagtttaatcagtcggttggtatcagggcgggggattgagggcgggggattgagggcgggtcaagggc
 4426 to 4500
 BbuI Zsp2I
 SphI
 NsiI

 NcoI Bsp19I
 StyI BstDSI
 EcoT14I
 BglI
 cccattctccgcccccatggctgactaatTTTTTTattatgcagagggccgagccctcggcctctgagctat
 base pairs
 gggtaagagggcgggtaccgactgattaaaaaaaaataaatcgtctccggctccggcgaggcggagactcgata
 4501 to 4575
 BstTlI
 SfiI
 ErhI Eco130I
 DsaI

FIG. 14-31

144/173

SseBI AvrII Ama87I
 Eco147I BlnI Eco88I BseRI
 StuI BstII AvaI BsoBI
 BseRI
 tccagaagtagtgaggaggcttttttggaggccctaggcttttgcaaaaagctc ctcgagggaactgaaaaaccaga
 base pairs
 aggtcttcacactcctccgaaaaaacctccggatccgaaaacgttttttcgag gagctccttgacttttttgggtct
 4576 to 4650

AatI StyI XhoI BcoI
 Pme55I ErhI Sfr274I
 EcoT14I Eco130I PaeR7I

SfiI ApoI
 aagttaattccctatagtgagtcgtatttaaattcgtaatcatggtcatagtgttctctgtgtgaaattgttatc
 base pairs
 ttcaattaagggatatacactcagcataaatttaagcatttagtaccagtatcgacaaaaggacacactttaacaatag
 4651 to 4725
 BstSFI AcsI

FIG. 14-32

AccBSI	AccBII
BsrBI	BshNI
cgctcacaattccacacaacatacgagccggaagcataaagtgtaaagcctgggggtgcctaataatgagtgcgtaac	
base pairs	
gcgagtgttaagggtgtgtatgctcggccttcgtatttcacatttcggacccccacggattactcactcgattg	
4726 to 4800	
BstD102I	BanI
	Eco64I
	145/173
VspI	VspI
PshBI	MspAII
	PvuII PshBI
	EaeI
tcacattaattgcgctcactgcccgctttccagtcgggaaacctgtcgtgccagctgcattaatgaatcg	
base pairs	
agtgtaatcaacgcgagtgacgggcgaaaaggtcagccctttggacagcacggtcgacgtaattacttagc	
4801 to 4875	
AsnI	NspBII
AseI	CfrI
	AsnI
	AseI

FIG. 14-33

146/173

Eam1104I
 BstH2I
 Bsp143II
 gccaacgcgcgggagaggggtttgcgtattgggcgctcttcggttcctcgctcactgactcgctgcgctcgg
 base pairs
 cggttgcgcgccccctctccgccaacgcataaacccgcgagaaaggagcgagtgactgagcgacgcgagcc
 4876 to 4950
 HaeII EarI
 SapI
 Ksp632I

BstMCI
 BsaOI
 AccBSI
 BsrBI
 tcgttcggctgcggcgagcgggtatcagctcactcaaggcggttaatacgggttatccacagaatcaggggataacg
 base pairs
 agcaagccgacgcgcgtcgccatagtcgagtgagttccgccattatgcccaatagggtgtcttagtccccctattgc
 4951 to 5025
 Bsh1285I
 BsiEI
 BstD102I

FIG. 14-34

147/173

NspI
BspLU11I
caggaagaacatgtgagcaaaaggccagcaaaaggccaggaaccgtaaaaaggccggttgctggcggtttttcc
base pairs
gtcctttcttgtaactcggtttccggtcggtttccggtccttggcatttttccggcggaacgacccgcaaaaagg
5026 to 5100
AflIII

DrdI
ataggctccgccccctgacgagcatcacaaaaatcgacgctcaagtcagagtgggcgaacccgacaggactat
base pairs
tatccgaggcgggggactgctcgtagtggttttagctcgaggttcagtctccaccgcttgggctgtcctgata
5101 to 5175

FIG. 14-35

148/173

BsaWI
 BsiI
 aaagataccaggcgtttccccctggaagctccctcgtgcgctctcctgttccgaccctgccgcttaccggatacc
 base pairs
 tttctatggtccgcaaaagggggaccttcgaggagcacgcgagagacaaggctgggacggcggaatggcctatgg
 5176 to 5250

BssSI

BstH2I
 Bsp143II
 SfiI
 tgtccgcctttctcccttcgggaagcgtggcgctttctcaatgctcacgctgtaggtatctcagttcgggtgtagg
 base pairs
 acaggcggaagagggaagcccttcgcacccgcgaaagagttacgagtgcgacatccatagagtcaagccacatcc
 5251 to 5325

HaeII BstSFI

FIG. 14-36

BsiHKAI NspBII
 Alw44I BstMCI
 VneI Bbv12I BsaOI BsaWI
 tcgttcgctccaagctgggctgtgtgcacgaaccccccggttcagcccgcacccgctgcgccttatccggtaactatc
 base pairs
 agcaagcgagggttcgacccgcacacacgtgcttggggggcaagtgggctggcgacgcgggaataggccattgatag
 5326 to 5400
 149/173
 ApaLI Bsh1285I
 AspHI BsiEI
 Alw21I MspA1I

AlwNI
 gtcttgagtcacaaccgggtaagacacgacttatcgccactggcagcagccactggtaacaggattagcagagcga
 base pairs
 cagaactcagggtgggccattctgtgctgaatagcgggtgaccgtcgtcggtgaccattgtcctaatacgtctcgtc
 5401 to 5475

FIG. 14-37

150/173

SfCI
ggtatgtaggcgggtgctacagagttcttgaagtggcctaactacggctacactagaagaacagtatattggta
base pairs
ccatacatccgcccacgatgtctcaagaacttcaccaccggattgatgccgatgtgatcttctgtcataaacccat
5476 to 5550

BstSFI

Eco57I
tctgcgctctgtgaagccagttaccttcggaaaaagagttggtagctcttgatccggcaaaaaccaccgctg
base pairs
agacgcgagacgacttcgggtcaatggaagccttttctcaaccatcgagaactaggccggttgttgggtggcgac
5551 to 5625

NspBII

MspAII

FIG. 14-38

MflI MflI
 XhoII XhoII
 gtagcgggtggtttttgtttgcaagcagcagattacgcgcagagaaaaaggatctcaagaagatccctttgatct
 base pairs
 catcgccacccaaaaaaacggttcgtcgtctaattgcggtcttttttccctagagttcttcttaggaaactaga
 5626 to 5700

BstYI BstYI
 BstX2I BstX2I

151/173

RcaI MflI
 XhoII
 tttctacgggtctgacgctcagtggaacgaaactcacgttaagggttttggtcatgagattatcaaaaaggga
 base pairs
 aaagatgccccagactgcgagtcaccttgcttttgagtgcgaattccctaaaaccagtactctaagtattttcct
 5701 to 5775

BspHI BstYI
 BstX2I

FIG. 14-39

152/173

MflI DraI
XhoII DraI
tcttcacctagatccttttaaattaaaaatgaagttttaaatcaatctaaagtatatatgagtaaaacttgggtctg
base pairs
agaagtggatctaggaaaaatttaatttttactttcaaaaatttagttagatttcatatatactcatttgaaccagac
5776 to 5850
BstYI
BstX2I

AccB1I
BshNI
acagttaccaatgctttaatcagtgaggcacctatctcagcgatctgtctatttcgttcatccatagttgcctgac
base pairs
tgtcaatgggttacgaatttagtcactccgtggatagagtcgctagacagataaaagcaagtaggtatcaacgggactg
5851 to 5925
BamI
Eco64I

FIG. 14-40

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Eam1105I
 AspEI
 BsrDI
 tccccgctgtagataactacgatacgggagggttaccatctggccccagtgtgcaatgataccgagagacc
 base pairs
 aggggcagcacatctattgatgctatgccctcccgaatggtagaccgggtcacgacgttactatggcgctctgg
 5926 to 6000
 EclHKI
 AhdI

Cfr10I
 BsaI BssAI BpmI BglI
 cagctcacccggctccagatttatcagcaataaacccagccggaaggccgagcagaagtgtcctgcaa
 base pairs
 gtgcgagtggccgaggtctaaatagtcgttatttggtcggtcggccttcccggctcgcgtcttcaccaggacgtt
 6001 to 6075
 Eco31I BsrFI GsuI
 Bse118I

FIG. 14-41

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VspI
PshBI
ctttatccgcctccatccagtcctattggtgcccgaagctagagtaagtagttgccagttaatagtttgc
base pairs
gaaataggcggaggtaggtcagataaattaacaacggcccttcgatctcattcatcaagcgtcaattatcaaacg
6076 to 6150

AsnI
AseI

AviII
FspI
gcaacgttggtgccattgctacaggcatcggtggtcacgctcgcttggtatggcttcattcagctccgggtt
base pairs
cgttgcaacaacggtaacgatgtccgtagcaccacagtgcgagcagcaaacccataccgaagtaagtcgagggccaa
6151 to 6225
Acc16I
Psp1406I
BstSFI
SfiI
MslI
BsaWI
BsrDI

FIG. 14-42

BsiEI
PvuI
BstMCI
BsaOI
cccaacgatcaaggcgagttacatgatcccccatgttggtgcaaaaaagcggtagctccttcggtcctccgatcg
base pairs
gggttgctagttccgctcaatgtactaggggtacaacacggttttttcgccaatcgaggaagccaggaggtacg
6226 to 6300

BspCI
Bsh1285I
Ple19I
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EaeI
MslI
ttgtcagaagtaagttggccgcagtggttatcactcatggttatggcagcactgcataattcttactgtcatgc
base pairs
aacagtccttcattcaaccggcggtcacaaatagtgagtaccacaataaccgtcgtgacgtattaaagagaatgacagtagc
6301 to 6375

CfrI

FIG. 14-43

Acc113I	BstMCI	
	BsaOI	
Eco255I		
catccgtaagatgcttttctgtgactgggtgagtactcaaccaagtcattctgagaatagtgatgcggcgaccca		
base pairs		
gtaggcattcttacgaaaagacacactgaccactcatgagttggttcagtaagactcttatcacatacgccgctggct		
6376 to 6450		
ScaI		
	Bsh1285I	
	BsiEI	
		156/173
BbiII	Alw21I	
HinII	AspHI	
BcgI	DraI	
gttgctcttgcccggcggtcaatacgggataataccgcgccacatagcagaacttttaaaagtgtcatcattggaa		
base pairs		
caacgagaaacggcgagttatgccctattatggcgcggtgtatcgctcttgaaattttcacgagtagtaacctt		
6451 to 6525		
Msp17I	BsiHKAI	
BsaHI	Bbv12I	
Hsp92I		

FIG. 14-44

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XmnI	MflI	MflI	BssSI
Psp1406I	XhoII	NspBII XhoII	Alw44I
aacgttcttcgggcgaaactctcaaggatcttaccgctgttgagatccagttcgatgtaaccactcgtgcac			VneI
base pairs			
ttgcaagaagccccgcttttgagagttcctagaatggcgacaactctaggtcaagctacattggggtgagcacgtg			
6526 to 6600			
Asp700I	BstYI	MspAII BstYI	ApalI
	BstX2I	BstX2I	BsiI
			AspHI

Bbv12I	Eco57I
BsiHKAI	
ccaaactgatcttcagcatcttttactttcaccagcgtttctgggtgagcaaaaacaggaaggcaaaatgccgcaa	
base pairs	
ggttgactagaagtcgtagaaaaatgaaagtgggtcgcaaaagaccactcgtttttgtccttccgttttaccggcgtt	
6601 to 6675	
Alw21I	

FIG. 14-45

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MslI EarI SspI
 aaaaagggaataagggcgacacgggaaatgttgaatactcatactcttccttttcaatatattatgaagcatttatac
 base pairs
 tttcccttattcccgctgtgcctttacaacttatgagtatgagaaggaaaaagttataataacttcgtaaatag
 6676 to 6750
 Ksp632I

AccBSI RcaI BsrBI
 agggttattgtctctcatgagcggatacatatttgaatgtatttagaaaaataaacaataaggggttccgcgcacat
 base pairs
 tcccaataacagagtactcgcctatgtataaaacttacataaatctttttattgtttatccccaaggcgcgtgta
 6751 to 6825
 BspHI BstD102I

FIG. 14-46

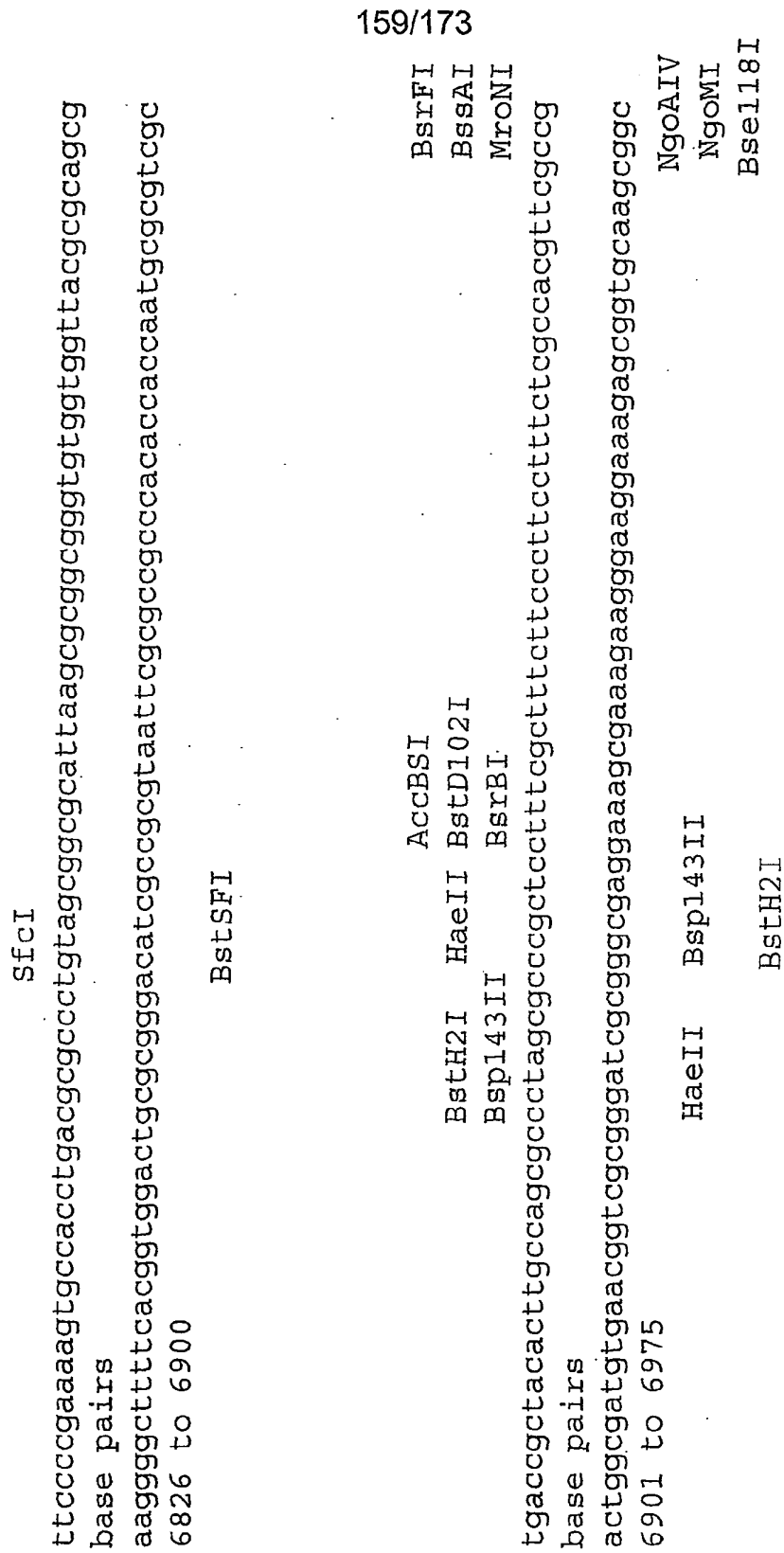


FIG. 14-47

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NaeI
gctttcccgtcaagctctaaatcggggcatcccttagggtccgatttagtgctttacggcacctcgacccca
base pairs
cgaaaggggcagttcgagatttagccccgtagggaatccccaggctaatacacgaaatgccgtggagctggggt
6976 to 7050

AccB1I
BshNI

BanI
Eco64I

Cfr10I

BsaAI
aaaaacttgattagggtgatggttcacgtagtgggccatgccctgatagacgggttttcgccctttgacgttgg
base pairs
ttttgaaactaatcccactaccacgaagtgcataccccggtagcgggactatctgcaaaaagcgggaaactgcaacc
7051 to 7125

DrdI

DraIII

FIG. 14-48

agtcacggtctttaatagtggaactctgttccaactggaacaacactcaaccctatctcgggtctattcttcttg
base pairs
tcagggtgcaagaattatcacctgagaacaagggttgaccttggtgtgagttgggatatagagccagataagaaaaac
7126 to 7200

atttataagggaatttgcggatttcggcctatttggttaaaaaatgagctgattttaacaaaaatttaacgcgaatt
base pairs
taaataattccctaaaaacggctaagccggataaccaattttttactcgactaaattgtttttaaatgcgcttaa
7201 to 7275

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ApoI ApoI

AcsI AcsI

SspI Psp1406I
ttaacaaaaatattaaacggtttacaattt base pairs
aattggttttataatttgcaaatgttaaa 7276 to 7303

FIG. 14-49

Table by Enzyme Name

Enzyme name	No. cuts	Positions of sites	Recognition sequence
AatI	2	3446 4606	agg/cct <u>More info</u>
AatII	5	451 504 587 773 4154	gacgt/c <u>More info</u>
Acc113I	1	6408	agt/act <u>More info</u>
Acc16I	2	21 6150	tgc/gca <u>More info</u>
Acc65I	3	2264 3434 3602	g/ gtacc <u>More info</u>
AccB1I	8	791 2264 3065 3434 3602 4779 5876 7036	g/ gyrcc <u>More info</u>
AccB7I	6	1445 1482 1775 1796 2644 4191	ccannnn/ntgg <u>More info</u>
AccBSI	4	4730 4971 6772 6936	gagcgg <u>More info</u>
Ac1NI	1	326	a/ ctagt <u>More info</u>
AcSI	7	912 1990 2244 2994 4679 7260 7271	r/ aatty <u>More info</u>
AcylI	6	448 501 584 770 4151 6465	gr/cgyc <u>More info</u>
Afl1I1I	2	2702 5035	a/ crygt <u>More info</u>
AgeI	1	4188	a/ ccggt <u>More info</u>
AhdI	2	3754 5928	gacnnn/nngtc <u>More info</u>
Alw21I	6	894 1576 2330 5353 6514 6599	gwgwc/c <u>More info</u>
Alw44I	2	5349 6595	g/ tgcac <u>More info</u>

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FIG. 14-50

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AlwNI	6	1147	1273	1775	3091	4282	5451	cagnnn/ctg	<u>More info</u>
Ama87I	3	3638	3934	4629				c/ ycgrg	<u>More info</u>
AocI	3	1034	1046	3256				cc/ tnagg	<u>More info</u>
Apal	1	3806						gggcc/c	<u>More info</u>
ApalI	2	5349	6595					g/ tgcac	<u>More info</u>
ApoI	7	912	1990	2244	2994	4679	7260	r/ aatty	<u>More info</u>
		7271							
AseI	4	334	4806	4865	6100			at/ taat	<u>More info</u>
AsnI	4	334	4806	4865	6100			at/ taat	<u>More info</u>
Asp700I	4	1107	2481	3506	6527			gaann/nnttc	<u>More info</u>
Asp718I	3	2264	3434	3602				g/ gtacc	<u>More info</u>
AspEI	2	3754	5928					gacnnn/nngtc	<u>More info</u>
AspHI	6	894	1576	2330	5353	6514	6599	gwgcw/c	<u>More info</u>
AvaI	3	3638	3934	4629				c/ ycgrg	<u>More info</u>
AviII	2	21	6150					tgc/gca	<u>More info</u>
AvrII	2	3109	4607					c/ ctagg	<u>More info</u>
BalI	4	184	238	3300	4018			tgg/cca	<u>More info</u>
BamHI	1	3596						g/ gatcc	<u>More info</u>
BanI	8	791	2264	3065	3434	3602	4779	g/ gyrcc	<u>More info</u>
		5876	7036						
BanII	6	894	1017	1623	3526	3558	3806	grgcy/c	<u>More info</u>
BanIII	1	939						at/ cgat	<u>More info</u>
BbiII	6	448	501	584	770	4151	6465	gr/cgyc	<u>More info</u>

FIG. 14-51

BbrPI	1	2705	cac/gtg	More info
BbsI	2	2512 3820	gaagac	More info
BbuI	4	2930 3959 4354 4427	gcatg/c	More info
Bbv12I	6	894 1576 2330 5353 6514 6599	gwgcw/c	More info
Bbv16II	2	2512 3820	gaagac	More info
BcgI	4	941 2556 3925 6455	cgannnnntgc	More info
BclI	1	969	t/ gatca	More info
BcoI	3	3638 3934 4629	c/ ycgrg	More info
BglI	5	14 417 538 4560 6048	gccnnnn/nggc	More info
BglII	2	932 3409	a/ gatct	More info
BlnI	2	3109 4607	c/ ctagg	More info
BlpI	3	1200 2337 3970	gc/tnagc	More info
BpiI	2	2512 3820	gaagac	More info
BpmI	9	1015 1279 1772 2781 2842 3022	ctggag	More info
		3701 3863 6018		
Bpu1102I	3	1200 2337 3970	gc/tnagc	More info
Bpu14I	3	1603 1988 2423	tt/cgaa	More info
BpuAI	2	2512 3820	gaagac	More info
Bsa29I	1	939	at/ cgat	More info
BsaAI	3	666 2705 7077	yac/gtr	More info
BsaHI	6	448 501 584 770 4151 6465	gr/cgyc	More info

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FIG. 14-52

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BsaI	3	3380	4031	6000	ggtctc	<u>More info</u>
BsaMI	1	1886			gaatgc	<u>More info</u>
BsaOI	7	42	424	928 4951 5375 6298 6447	cgry/cg	<u>More info</u>
BsaWI	6	3200	3599	4188 5241 5388 6219	w/ ccgww	<u>More info</u>
BsCI	1	939			at/ cgat	<u>More info</u>
Bse118I	3	4188	6008	6972	r/ ccggy	<u>More info</u>
Bse21I	3	1034	1046	3256	cc/ tnagg	<u>More info</u>
BseCI	1	939			at/ cgat	<u>More info</u>
BseRI	4	1337	1671	4593 4631	gaggag	<u>More info</u>
BsgI	3	2315	3212	3868	gtgcag	<u>More info</u>
Bsh1285I	7	42	424	928 4951 5375 6298 6447	cgry/cg	<u>More info</u>
BshNI	8	791	2264	3065 3434 3602 4779	g/ gyrcc	<u>More info</u>
		5876	7036			
BsiEI	7	42	424	928 4951 5375 6298 6447	cgry/cg	<u>More info</u>
BsiHKAI	6	894	1576	2330 5353 6514 6599	gwgcw/c	<u>More info</u>
BsiI	2	5213	6597		ctcgtg	<u>More info</u>
BsmBI	3	2023	2773	4001	cgtctc	<u>More info</u>
BsmI	1	1886			gaatgc	<u>More info</u>
BsoBI	3	3638	3934	4629	c/ ycgrg	<u>More info</u>
Bsp106I	1	939			at/ cgat	<u>More info</u>
Bsp119I	3	1603	1988	2423	tt/cgaa	<u>More info</u>
Bsp120I	1	3802			g/ ggccc	<u>More info</u>
Bsp1407I	2	270	3471		t/ gtaca	<u>More info</u>

FIG. 14-53

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Bsp143II	5	2519	4913	5283	6922	6930	rgcgc/y	<u>More info</u>
Bsp1720I	3	1200	2337	3970			gc/tnagc	<u>More info</u>
Bsp19I	5	686	3324	3424	4178	4514	c/ catgg	<u>More info</u>
BspCI	2	42	6298				cgat/cg	<u>More info</u>
BspDI	1	939					at/ cgat	<u>More info</u>
BspHI	3	1891	5755	6763			t/ catga	<u>More info</u>
BspLU11I	1	5035					a/ catgt	<u>More info</u>
BspMI	2	1913	4178				acctgc	<u>More info</u>
BspXI	1	939					at/ cgat	<u>More info</u>
BsrBI	4	4730	4971	6772	6936		gagcgg	<u>More info</u>
BsrDI	5	245	2827	3594	5987	6169	gcaatg	<u>More info</u>
BsrFI	3	4188	6008	6972			r/ ccggy	<u>More info</u>
BsrGI	2	270	3471				t/ gtaca	<u>More info</u>
BssAI	3	4188	6008	6972			r/ ccggy	<u>More info</u>
BssSI	2	5213	6597				ctcgtg	<u>More info</u>
BsST1I	11	686	1950	2226	3109	3324 3424	c/ cwwgg	<u>More info</u>
		3681	4060	4178	4514	4607		
BstBI	3	1603	1988	2423			tt/cgaa	<u>More info</u>
BstD102I	4	4730	4971	6772	6936		gagcgg	<u>More info</u>
BstDSI	6	686	1062	3324	3424	4178 4514	c/ crygg	<u>More info</u>
BstH2I	5	2519	4913	5283	6922	6930	rgcgc/y	<u>More info</u>
BstI	1	3596					g/ gatcc	<u>More info</u>

FIG. 14-54

BstMCI	7	42 424 928 4951 5375 6298 6447	cgry/cg	<u>More info</u>
BstSFI	8	944 2144 3824 4662 5300 5491	c/ tryag	<u>More info</u>
		6169 6854		
BstSNI	1	666	tac/gta	<u>More info</u>
BstX2I	12	932 2400 2634 3409 3596 3634	r/ gatcy	<u>More info</u>
		5676 5687 5773 5785 6553 6570		
BstXI	3	3076 3325 4077	ccannnnn/ntgg	<u>More info</u>
BstYI	12	932 2400 2634 3409 3596 3634	r/ gatcy	<u>More info</u>
		5676 5687 5773 5785 6553 6570		
BstZI	1	925	c/ ggccg	<u>More info</u>
Bsu15I	1	939	at/ cgat	<u>More info</u>
Bsu36I	3	1034 1046 3256	cc/ tnagg	<u>More info</u>
CciNI	1	925	gc/ggccgc	<u>More info</u>
CelII	3	1200 2337 3970	gc/tnagc	<u>More info</u>
Cfr10I	3	4188 6008 6972	r/ ccggy	<u>More info</u>
Cfr9I	1	3638	c/ ccggg	<u>More info</u>
CfrI	9	152 182 236 925 3298 4016 4273	y/ ggccr	<u>More info</u>
		4874 6316		
Clai	1	939	at/ cgat	<u>More info</u>
Csp45I	3	1603 1988 2423	tt/cgaa	<u>More info</u>
Cvni	3	1034 1046 3256	cc/ tnagg	<u>More info</u>

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FIG. 14-55

DraI	4	4127	5794	5813	6505	ttt/aaa	More info
DraII	3	3291	3802	3829		rg/gnccy	More info
DraIII	1	7080				cacnnn/gtg	More info
DrdI	3	1076	5143	7124		gacnnnn/nngtc	More info
DsaI	6	686	1062	3324	3424 4178 4514	c/ crygg	More info
EaeI	9	152	182	236	925 3298 4016 4273	y/ ggccr	More info
		4874	6316				
EagI	1	925				c/ ggccg	More info
Eam1104I	5	58	2482	2793	4918 6722	ctcttc	More info
Eam1105I	2	3754	5928			gacnnn/nngtc	More info
EarI	5	58	2482	2793	4918 6722	ctcttc	More info
Ecl136II	1	892				gag/ ctc	More info
EclHKI	2	3754	5928			gacnnn/nngtc	More info
EclXI	1	925				c/ ggccg	More info
Eco105I	1	666				tac/gta	More info
Eco130I	11	686	1950	2226	3109 3324 3424	c/ cwwgg	More info
		3681	4060	4178	4514 4607		
Eco147I	2	3446	4606			agg/cct	More info
Eco24I	6	894	1017	1623	3526 3558 3806	grgcy/c	More info
Eco255I	1	6408				agt/act	More info
Eco31I	3	3380	4031	6000		ggtctc	More info
Eco32I	1	952				gat/ atc	More info
Eco52I	1	925				c/ ggccg	More info

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FIG. 14-56

Eco57I	7	1210 2446 2488 3271 3314 5567 6615	ctgaag	<u>More info</u>
Eco64I	8	791 2264 3065 3434 3602 4779 5876 7036	g/ gyrcc	<u>More info</u>
Eco72I	1	2705	cac/gtg	<u>More info</u>
Eco81I	3	1034 1046 3256	cc/ tnagg	<u>More info</u>
Eco88I	3	3638 3934 4629	c/ ycgrg	<u>More info</u>
EcoICRI	1	892	gag/ ctc	<u>More info</u>
EcoNI	3	1259 1338 1684	cctnn/nnnagg	<u>More info</u>
EcoO109I	3	3291 3802 3829	rg/gnccy	<u>More info</u>
EcoRI	3	912 1990 2994	g/ aattc	<u>More info</u>
EcoRV	1	952	gat/ atc	<u>More info</u>
EcoT14I	11	686 1950 2226 3109 3324 3424 3681 4060 4178 4514 4607	c/ cwwgg	<u>More info</u>
EcoT22I	3	3961 4356 4429	atgca/t	<u>More info</u>
ErhI	11	686 1950 2226 3109 3324 3424 3681 4060 4178 4514 4607	c/ cwwgg	<u>More info</u>
Esp1396I	6	1445 1482 1775 1796 2644 4191	ccannnn/ntgg	<u>More info</u>
Esp3I	3	2023 2773 4001	cgtctc	<u>More info</u>
FauNDI	1	560	ca/ tatg	<u>More info</u>
FbaI	1	969	t/ gatca	<u>More info</u>
FriOI	6	894 1017 1623 3526 3558 3806	grgcy/c	<u>More info</u>
FspI	2	21 6150	tgc/gca	<u>More info</u>

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FIG. 14-57

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GsuI	9	1015 1279 1772 2781 2842 3022	ctggag	<u>More info</u>
HaeII	5	3701 3863 6018	rgcgc/y	<u>More info</u>
HinII	6	2519 4913 5283 6922 6930	gr/cgyc	<u>More info</u>
HincII	3	448 501 584 770 4151 6465	gty/rac	<u>More info</u>
HindII	3	311 446 842	gty/rac	<u>More info</u>
HindIII	3	311 446 842	a/ agctt	<u>More info</u>
Hsp92I	6	918 1394 2183	gr/cgyc	<u>More info</u>
KpnI	3	448 501 584 770 4151 6465	ggtac/c	<u>More info</u>
Ksp22I	1	2268 3438 3606	t/ gatca	<u>More info</u>
Ksp632I	5	969	ctcttc	<u>More info</u>
LspI	3	58 2482 2793 4918 6722	tt/cgaa	<u>More info</u>
MfeI	1	1603 1988 2423	c/ aattg	<u>More info</u>
MflI	12	1091	r/ gatcy	<u>More info</u>
MluNI	4	932 2400 2634 3409 3596 3634	tgg/cca	<u>More info</u>
Mph1103I	3	5676 5687 5773 5785 6553 6570	atgca/t	<u>More info</u>
MronI	1	184 238 3300 4018	g/ ccggc	<u>More info</u>
MscI	4	3961 4356 4429	tgg/cca	<u>More info</u>
MslI	10	6972	caynn/nnrtg	<u>More info</u>
Msp17I	6	184 238 3300 4018	gr/cgyc	<u>More info</u>
MspA1I	7	691 2094 2703 3323 3489 3651	cmg/ckg	<u>More info</u>
		3698 6180 6339 6698		
		448 501 584 770 4151 6465		
		71 2341 2731 4859 5377 5622 6563		

FIG. 14-58

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MunI	1	1091		c/ aattg	More info
MvaI269I	1	1886		gaatgc	More info
NaeI	1	6974		gcc/ggc	More info
NcoI	5	686	3324 3424 4178 4514	c/ catgg	More info
NdeI	1	560		ca/ tatg	More info
NgoAIV	1	6972		g/ ccggc	More info
NgomI	1	6972		g/ ccggc	More info
NotI	1	925		gc/ggccgc	More info
NsiI	3	3961	4356 4429	atgca/t	More info
NspBII	7	71	2341 2731 4859 5377 5622 6563	cmg/ckg	More info
NspI	5	2930	3959 4354 4427 5039	rcatg/y	More info
NspV	3	1603	1988 2423	tt/cgaa	More info
PaeI	4	2930	3959 4354 4427	gcatg/c	More info
Paer7I	1	4629		c/ tcgag	More info
PflMI	6	1445	1482 1775 1796 2644 4191	ccannnn/ntgg	More info
PinAI	1	4188		a/ ccggt	More info
Ple19I	2	42	6298	cgat/cg	More info
PmaCI	1	2705		cac/gtg	More info
Pme55I	2	3446	4606	agg/cct	More info
PmlI	1	2705		cac/gtg	More info
Ppu10I	3	3957	4352 4425	a/ tgcac	More info
PshBI	4	334	4806 4865 6100	at/ taat	More info
Psp124BI	1	894		gagct/c	More info
Psp1406I	3	6154	6527 7291	aa/cgtt	More info

FIG. 14-59

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PspAI	1	3638		c/ ccggg	More info
PspALI	1	3640		ccc/ggg	More info
PspOMI	1	3802		g/ ggccc	More info
PstI	2	948 2148		ctgca/g	More info
PvuI	2	42 6298		cgat/cg	More info
PvuII	3	71 2341 4859		cag/ctg	More info
RcaI	3	1891 5755 6763		t/ catga	More info
SacI	1	894		gagct/c	More info
SapI	2	2483 4918		gctcttc	More info
ScaI	1	6408		agt/act	More info
SexAI	1	4373		a/ ccwgg	More info
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Sfr274I	1	4629		c/ tcgag	More info
SfuI	3	1603 1988 2423		tt/cgaa	More info
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SnaBI	1	666		tac/gta	More info
SpeI	1	326		a/ ctagt	More info
SphI	4	2930 3959 4354 4427		gcatg/c	More info
SseBI	2	3446 4606		agg/cct	More info
SspBI	2	270 3471		t/ gtaca	More info
SspI	5	179 226 3768 6732 7285		aat/att	More info
SstI	1	894		gagct/c	More info

FIG. 14-60

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AccI, AccIII, AfeI, AFLII, Aor51HI, AscI, AspI, AtSI, BbeI, BfrI, BsaBI, Bse8I, BseAI, BsePI, Bsh1365I, BsiMI, BsiWI, Bsp13I, Bsp68I, BspEI, BspTI, BsrBRI, BssHII, Bst1107I, Bst98I, BstEII, BstPI, Cfr42I, CpoI, CspI, Eco47III, Eco91I, EcoO65I, EheI, FseI, HpaI, Kasi, Kpn2I, KspI, Mami, MluI, MroI, MspCI, Nari, NheI, NruI, PacI, Pfl23II, PmeI, PpuMI, PshAI, Psp5II, PspEI, PspLI, PstNHI, RsrII, SacII, SalI, SbfI, Sfr303I, Sgfi, SgrAI, SmiI, SplI, SrfI, Sse8387I, SSstII, SunI, SwaI, Tth11I, Vha464I, XbaI

FIG. 14-61

SEQUENCE LISTING

<110> Sloan-Kettering Institute for Cancer Research
Richon, Victoria
Zhou, Xianbo
Rifkind, Richard A.
Marks, Paul A.

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and Uses Thereof

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50 55 60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
65 70 75 80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Ala Ile Lys Gln Gln
85 90 95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
100 105 110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
115 120 125
Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
130 135 140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
145 150 155 160
Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
165 170 175
Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
180 185 190
Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
195 200 205
Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Ala Ser Glu Pro Asn Leu
210 215 220
Lys Val Arg Ser Arg Leu Lys Gln Lys Val Ala Glu Arg Arg Ser Ser
225 230 235 240

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Ser	Gly	Pro	Ser	Ser	Pro	Asn	Asn	Gly	Pro	Thr	Gly	Ser	Val	Thr	Glu
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Asn	Glu	Thr	Ser	Val	Leu	Pro	Pro	Thr	Pro	His	Ala	Glu	Gln	Met	Val
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Ser	Gln	Gln	Arg	Ile	Leu	Ile	His	Glu	Asp	Ser	Met	Asn	Leu	Leu	Ser
305				310						315					320
Leu	Tyr	Thr	Ser	Pro	Ser	Leu	Pro	Asn	Ile	Thr	Leu	Gly	Leu	Pro	Ala
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Cys	Glu	Thr	Gln	Thr	Leu	Arg	Gln	Gly	Val	Pro	Leu	Pro	Gly	Gln	Tyr
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Gly	Gly	Ser	Ile	Pro	Ala	Ser	Ser	Ser	His	Pro	His	Val	Thr	Leu	Glu
	370					375					380				
Gly	Lys	Pro	Pro	Asn	Ser	Ser	His	Gln	Ala	Leu	Leu	Gln	His	Leu	Leu
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Leu	Lys	Glu	Gln	Met	Arg	Gln	Gln	Lys	Leu	Leu	Val	Ala	Gly	Gly	Val
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Pro	Leu	His	Pro	Gln	Ser	Pro	Leu	Ala	Thr	Lys	Glu	Arg	Ile	Ser	Pro
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Gly	Ile	Arg	Gly	Thr	His	Lys	Leu	Pro	Arg	His	Arg	Pro	Leu	Asn	Arg
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Thr	Gln	Ser	Ala	Pro	Leu	Pro	Gln	Ser	Thr	Leu	Ala	Gln	Leu	Val	Ile
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465				470						475					480
Gln	Ile	His	Met	Asn	Lys	Leu	Leu	Ser	Lys	Ser	Ile	Glu	Gln	Leu	Lys
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Leu	Glu	Pro	Thr	His	Thr	Arg	Ala	Leu	Ser	Val	Arg	Gln	Ala	Pro	Leu
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Ala	Ala	Val	Gly	Met	Asp	Gly	Leu	Glu	Lys	His	Arg	Leu	Val	Ser	Arg
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Asn	Pro	Leu	Asp	Gly	Gln	Lys	Leu	Asp	Pro	Arg	Ile	Leu	Leu	Gly	Asp
705					710					715					720
Asp	Ser	Gln	Lys	Phe	Phe	Ser	Ser	Leu	Pro	Cys	Gly	Gly	Leu	Gly	Val
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 885 890 895
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Glu Leu Leu Leu Ile Gln Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
50      55      60
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65      70      75      80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
85      90      95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
100     105     110

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Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
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 Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
 130 135 140
 Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
 145 150 155 160
 Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
 165 170 175
 Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
 180 185 190
 Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
 195 200 205
 Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Ala Ser Glu Pro Asn Leu
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 Lys Val Arg Ser Arg Leu Lys Gln Lys Val Ala Glu Arg Arg Ser Ser
 225 230 235 240
 Pro Leu Leu Arg Arg Lys Asp Gly Asn Val Val Thr Ser Phe Lys Lys
 245 250 255
 Arg Met Phe Glu Val Thr Glu Ser Ser Val Ser Ser Ser Pro Gly
 260 265 270
 Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly Ser Val Thr Glu
 275 280 285
 Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala Glu Gln Met Val
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 Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met Asn Leu Leu Ser
 305 310 315 320
 Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu Gly Leu Pro Ala
 325 330 335
 Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys Glu Lys Gln Lys
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 Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu Pro Gly Gln Tyr
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 Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His Val Thr Leu Glu
 370 375 380
 Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu Gln His Leu Leu
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 Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu Arg Ile Ser Pro
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 Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg Pro Leu Asn Arg
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 Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala Gln Leu Val Ile
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 Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile Glu Gln Leu Lys
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 Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu Leu Gln Gly Asp
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 Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly Asn Ser Thr Arg
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 Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu Asp Ala Gln Ile
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 Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met Gln Gln Pro Phe
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 Leu Glu Pro Thr His Thr Arg Ala Leu Ser Val Arg Gln Ala Pro Leu
 580 585 590
 Ala Ala Val Gly Met Asp Gly Leu Glu Lys His Arg Leu Val Ser Arg
 595 600 605

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Thr His Ser Ser Pro Ala Ala Ser Val Leu Pro His Pro Ala Met Asp
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 Arg Pro Leu Gln Pro Gly Ser Ala Thr Gly Ile Ala Tyr Asp Pro Leu
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 Met Leu Lys His Gln Cys Val Cys Gly Asn Ser Thr Thr His Pro Glu
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 His Ala Gly Arg Ile Gln Ser Ile Trp Ser Arg Leu Gln Glu Thr Gly
 660 665 670
 Leu Leu Asn Lys Cys Glu Arg Ile Gln Gly Arg Lys Ala Ser Leu Glu
 675 680 685
 Glu Ile Gln Leu Val His Ser Glu His His Ser Leu Leu Tyr Gly Thr
 690 695 700
 Asn Pro Leu Asp Gly Gln Lys Leu Asp Pro Arg Ile Leu Leu Gly Asp
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 Asp Ser Gln Lys Phe Phe Ser Ser Leu Pro Cys Gly Gly Leu Gly Val
 725 730 735
 Asp Ser Asp Thr Ile Trp Asn Glu Leu His Ser Ser Gly Ala Ala Arg
 740 745 750
 Met Ala Val Gly Cys Val Ile Glu Leu Ala Ser Lys Val Ala Ser Gly
 755 760 765
 Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro Gly His His Ala
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 Glu Glu Ser Thr Ala Met Gly Phe Cys Phe Phe Asn Ser Val Ala Ile
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 Thr Ala Lys Tyr Leu Arg Asp Gln Leu Asn Ile Ser Lys Ile Leu Ile
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 Val Asp Leu Asp Val His His Gly Asn Gly Thr Gln Gln Ala Phe Tyr
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 Ala Asp Pro Ser Ile Leu Tyr Ile Ser Leu His Arg Tyr Asp Glu Gly
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<211> 3054

<212> DNA

<213> Homo sapiens

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 cttcttatcc agcagcagca acaaaccag aagcagcttc tgatagcaga gtttcagaaa 360
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<212> PRT
<213> Homo sapiens

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35          40          45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
50          55          60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
65          70          75          80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
85          90          95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
100          105          110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
115          120          125
Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
130          135          140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
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Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
165          170          175
Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Leu
180          185          190

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Glu	Gln	Met	Val	Ser	Gln	Gln	Arg	Ile	Leu	Ile	His	Glu	Asp	Ser	Met		
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Asn	Leu	Leu	Ser	Leu	Tyr	Thr	Ser	Pro	Ser	Leu	Pro	Asn	Ile	Thr	Leu		
		275					280					285					
Gly	Leu	Pro	Ala	Val	Pro	Ser	Gln	Leu	Asn	Ala	Ser	Asn	Ser	Leu	Lys		
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Pro	Gly	Gln	Tyr	Gly	Gly	Ser	Ile	Pro	Ala	Ser	Ser	Ser	His	Pro	His		
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Val	Thr	Leu	Glu	Gly	Lys	Pro	Pro	Asn	Ser	Ser	His	Gln	Ala	Leu	Leu		
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Gln	His	Leu	Leu	Lys	Glu	Gln	Met	Arg	Gln	Gln	Lys	Leu	Leu	Val			
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Ala	Gly	Gly	Val	Pro	Leu	His	Pro	Gln	Ser	Pro	Leu	Ala	Thr	Lys	Glu		
		370				375					380						
Arg	Ile	Ser	Pro	Gly	Ile	Arg	Gly	Thr	His	Lys	Leu	Pro	Arg	His	Arg		
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Pro	Leu	Asn	Arg	Thr	Gln	Ser	Ala	Pro	Leu	Pro	Gln	Ser	Thr	Leu	Ala		
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Gln	Leu	Val	Ile	Gln	Gln	Gln	His	Gln	Gln	Phe	Leu	Glu	Lys	Gln	Lys		
		420						425					430				
Gln	Tyr	Gln	Gln	Gln	Ile	His	Met	Asn	Lys	Leu	Leu	Ser	Lys	Ser	Ile		
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Glu	Gln	Leu	Lys	Gln	Pro	Gly	Ser	His	Leu	Glu	Glu	Ala	Glu	Glu	Glu		
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Leu	Gln	Gly	Asp	Gln	Ala	Met	Gln	Glu	Asp	Arg	Ala	Pro	Ser	Ser	Gly		
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Asn	Ser	Thr	Arg	Ser	Asp	Ser	Ser	Ala	Cys	Val	Asp	Asp	Thr	Leu	Gly		
				485					490					495			
Gln	Val	Gly	Ala	Val	Lys	Val	Lys	Glu	Glu	Pro	Val	Asp	Ser	Asp	Glu		
				500				505					510				
Asp	Ala	Gln	Ile	Gln	Glu	Met	Glu	Ser	Gly	Glu	Gln	Ala	Ala	Phe	Met		
		515					520					525					
Gln	Gln	Pro	Phe	Leu	Glu	Pro	Thr	His	Thr	Arg	Ala	Leu	Ser	Val	Arg		
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Gln	Ala	Pro	Leu	Ala	Ala	Val	Gly	Met	Asp	Gly	Leu	Glu	Lys	His	Arg		
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Leu	Val	Ser	Arg	Thr	His	Ser	Ser	Pro	Ala	Ala	Ser	Val	Leu	Pro	His		
				565					570					575			
Pro	Ala	Met	Asp	Arg	Pro	Leu	Gln	Pro	Gly	Ser	Ala	Thr	Gly	Ile	Ala		
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Tyr	Asp	Pro	Leu	Met	Leu	Lys	His	Gln	Cys	Val	Cys	Gly	Asn	Ser	Thr		
		595					600					605					
Thr	His	Pro	Glu	His	Ala	Gly	Arg	Ile	Gln	Ser	Ile	Trp	Ser	Arg	Leu		
		610				615					620						
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Leu	Tyr	Gly	Thr	Asn	Pro	Leu	Asp	Gly	Gln	Lys	Leu	Asp	Pro	Arg	Ile		
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Leu	Leu	Gly	Asp	Asp	Ser	Gln	Lys	Phe	Phe	Ser	Ser	Leu	Pro	Cys	Gly		
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 Gly Ala Ala Arg Met Ala Val Gly Cys Val Ile Glu Leu Ala Ser Lys
 705 710 715 720
 Val Ala Ser Gly Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro
 725 730 735
 Gly His His Ala Glu Glu Ser Thr Ala Met Gly Phe Cys Phe Phe Asn
 740 745 750
 Ser Val Ala Ile Thr Ala Lys Tyr Leu Arg Asp Gln Leu Asn Ile Ser
 755 760 765
 Lys Ile Leu Ile Val Asp Leu Asp Val His His Gly Asn Gly Thr Gln
 770 775 780
 Gln Ala Phe Tyr Ala Asp Pro Ser Ile Leu Tyr Ile Ser Leu His Arg
 785 790 795 800
 Tyr Asp Glu Gly Asn Phe Phe Pro Gly Ser Gly Ala Pro Asn Glu Val
 805 810 815
 Gly Thr Gly Leu Gly Glu Gly Tyr Asn Ile Asn Ile Ala Trp Thr Gly
 820 825 830
 Gly Leu Asp Pro Pro Met Gly Asp Val Glu Tyr Leu Glu Ala Phe Arg
 835 840 845
 Thr Ile Val Lys Pro Val Ala Lys Glu Phe Asp Pro Asp Met Val Leu
 850 855 860
 Val Ser Ala Gly Phe Asp Ala Leu Glu Gly His Thr Pro Pro Leu Gly
 865 870 875 880
 Gly Tyr Lys Val Thr Ala Lys Cys Phe Gly His Leu Thr Lys Gln Leu
 885 890 895
 Met Thr Leu Ala Asp Gly Arg Val Val Leu Ala Leu Glu Gly Gly His
 900 905 910
 Asp Leu Thr Ala Ile Cys Asp Ala Ser Glu Ala Cys Val Asn Ala Leu
 915 920 925
 Leu Gly Asn Glu Leu Glu Pro Leu Ala Glu Asp Ile Leu His Gln Ser
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 <213> Homo sapiens

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3367

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<211> 835

<212> PRT

<213> Homo sapiens

<400> 8

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35     40     45
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50     55     60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
65     70     75     80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
85     90     95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
100    105    110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
115    120    125

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Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
 130 135 140
 Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
 145 150 155 160
 Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
 165 170 175
 Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
 180 185 190
 Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
 195 200 205
 Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Glu Ser Ser Val Ser Ser
 210 215 220
 Ser Ser Pro Gly Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly
 225 230 235 240
 Ser Val Thr Glu Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala
 245 250 255
 Glu Gln Met Val Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met
 260 265 270
 Asn Leu Leu Ser Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu
 275 280 285
 Gly Leu Pro Ala Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys
 290 295 300
 Glu Lys Gln Lys Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu
 305 310 315 320
 Pro Gly Gln Tyr Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His
 325 330 335
 Val Thr Leu Glu Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu
 340 345 350
 Gln His Leu Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val
 355 360 365
 Ala Gly Gly Val Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu
 370 375 380
 Arg Ile Ser Pro Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg
 385 390 395 400
 Pro Leu Asn Arg Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala
 405 410 415
 Gln Leu Val Ile Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys
 420 425 430
 Gln Tyr Gln Gln Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile
 435 440 445
 Glu Gln Leu Lys Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu
 450 455 460
 Leu Gln Gly Asp Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly
 465 470 475 480
 Asn Ser Thr Arg Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly
 485 490 495
 Gln Val Gly Ala Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu
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 Asp Ala Gln Ile Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met
 515 520 525
 Gln Gln Pro Phe Leu Glu Pro Thr His Thr Arg Ala Leu Ser Val Arg
 530 535 540
 Gln Ala Pro Leu Ala Ala Val Gly Met Asp Gly Leu Glu Lys His Arg
 545 550 555 560
 Leu Val Ser Arg Thr His Ser Ser Pro Ala Ala Ser Val Leu Pro His
 565 570 575
 Pro Ala Met Asp Arg Pro Leu Gln Pro Gly Ser Ala Thr Gly Ile Ala
 580 585 590
 Tyr Asp Pro Leu Met Leu Lys His Gln Cys Val Cys Gly Asn Ser Thr
 595 600 605
 Thr His Pro Glu His Ala Gly Arg Ile Gln Ser Ile Trp Ser Arg Leu
 610 615 620

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Gln Glu Thr Gly Leu Leu Asn Lys Cys Glu Arg Ile Gln Gly Arg Lys
 625 630 635 640
 Ala Ser Leu Glu Glu Ile Gln Leu Val His Ser Glu His His Ser Leu
 645 650 655
 Leu Tyr Gly Thr Asn Pro Leu Asp Gly Gln Lys Leu Asp Pro Arg Ile
 660 665 670
 Leu Leu Gly Asp Asp Ser Gln Lys Phe Phe Ser Ser Leu Pro Cys Gly
 675 680 685
 Gly Leu Gly Val Asp Ser Asp Thr Ile Trp Asn Glu Leu His Ser Ser
 690 695 700
 Gly Ala Ala Arg Met Ala Val Gly Cys Val Ile Glu Leu Ala Ser Lys
 705 710 715 720
 Val Ala Ser Gly Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro
 725 730 735
 Gly His His Ala Glu Glu Ser Thr Ala Met Gly Phe Cys Phe Phe Asn
 740 745 750
 Ser Val Ala Ile Thr Ala Lys Tyr Leu Arg Asp Gln Leu Asn Ile Ser
 755 760 765
 Lys Ile Leu Ile Val Asp Leu Asp Val His His Gly Asn Gly Thr Gln
 770 775 780
 Gln Ala Phe Tyr Ala Asp Pro Ser Ile Leu Tyr Ile Ser Leu His Arg
 785 790 795 800
 Tyr Asp Glu Gly Asn Phe Phe Pro Gly Ser Gly Ala Pro Asn Glu Val
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 Cys Ile Ala
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<211> 1791

<212> DNA

<213> Homo sapiens

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 aagtcagaag ttctgtggg cctggagccc atctcacctt tagacctaa gacagacctc 240
 aggatgatga tgcccggtgt ggacctgtt gtccgtgaga agcaattgca gcaggaatta 300
 ctctttatcc agcagcagca acaaatccag aagcagcttc tgatagcaga gtttcagaaa 360
 cagcatgaga acttgacacg gcagcaccag gctcagcttc aggagcatat caaggaactt 420
 ctagccataa aacagcaaca agaactccta gaaaaggagc agaaactgga gcagcagagg 480
 caagaacagg aagtagagag gcatcgagca gaacagcagc ttctcctct cagaggcaaa 540
 gatagaggac gagaaagggc agtggcaagt acagaagtaa agcagaagct tcaagagttc 600
 ctactgagta aatcagcaac gaaagacact ccaactaatg gaaaaaatca ttccgtgagc 660
 cgccatccca agctctggtg cagggtgcc caccacacat cattggatca aagctctcca 720
 ccccttagtg gaacatctcc atctacaag tacacattac caggagcaca agatgcaaag 780
 gatgatttcc ccttcgaaa aactgaatcc tcagtcagta gcagttctcc aggcctctgt 840
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gtggatgaca cactgggaca agttggggct gtgaagggtca aggaggaacc agtggacagt 1680
gatgaagatg ctcagatcca ggaaatggaa tctgggggagc aggctgcttt tatgcaacag 1740
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<211> 546

<212> PRT

<213> Homo sapiens

<400> 10

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Met Met Pro Val Val Asp Pro Val Arg Glu Lys Gln Leu Gln Gln
 35      40      45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
 50      55      60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
 65      70      75      80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
 85      90      95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
100      105      110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
115      120      125
Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
130      135      140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
145      150      155      160
Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
165      170      175
Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
180      185      190
Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
195      200      205
Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Glu Ser Ser Val Ser Ser
210      215      220
Ser Ser Pro Gly Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly
225      230      235      240
Ser Val Thr Glu Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala
245      250      255
Glu Gln Met Val Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met
260      265      270
Asn Leu Leu Ser Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu
275      280      285
Gly Leu Pro Ala Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys
290      295      300
Glu Lys Gln Lys Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu
305      310      315      320
Pro Gly Gln Tyr Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His
325      330      335
Val Thr Leu Glu Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu
340      345      350
Gln His Leu Leu Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val
355      360      365
Ala Gly Gly Val Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu
370      375      380
Arg Ile Ser Pro Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg
385      390      395      400
Pro Leu Asn Arg Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala

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405 410 415
 Gln Leu Val Ile Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys
 420 425 430
 Gln Tyr Gln Gln Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile
 435 440 445
 Glu Gln Leu Lys Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu
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 Leu Gln Gly Asp Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly
 465 470 475 480
 Asn Ser Thr Arg Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly
 485 490 495
 Gln Val Gly Ala Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu
 500 505 510
 Asp Ala Gln Ile Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met
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 Ile Ile
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 <212> PRT
 <213> Homo sapiens

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 35 40 45
 Glu Leu Leu Leu Ile Gln Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
 50 55 60
 Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
 65 70 75 80
 Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
 85 90 95
 Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
 100 105 110
 Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
 115 120 125
 Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
 130 135 140
 Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
 145 150 155 160
 Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
 165 170 175
 Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
 180 185 190
 Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
 195 200 205
 Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Ala Ser Glu Pro Asn Leu
 210 215 220
 Lys Val Arg Ser Arg Leu Lys Gln Lys Val Ala Glu Arg Arg Ser Ser
 225 230 235 240
 Pro Leu Leu Arg Arg Lys Asp Gly Asn Val Val Thr Ser Phe Lys Lys
 245 250 255
 Arg Met Phe Glu Val Thr Glu Ser Ser Val Ser Ser Ser Ser Pro Gly
 260 265 270
 Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly Ser Val Thr Glu

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275 280 285
 Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala Glu Gln Met Val
 290 295 300
 Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met Asn Leu Leu Ser
 305 310 315 320
 Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu Gly Leu Pro Ala
 325 330 335
 Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys Glu Lys Gln Lys
 340 345 350
 Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu Pro Gly Gln Tyr
 355 360 365
 Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His Val Thr Leu Glu
 370 375 380
 Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu Gln His Leu Leu
 385 390 395 400
 Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val Ala Gly Gly Val
 405 410 415
 Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu Arg Ile Ser Pro
 420 425 430
 Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg Pro Leu Asn Arg
 435 440 445
 Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala Gln Leu Val Ile
 450 455 460
 Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys Gln Tyr Gln Gln
 465 470 475 480
 Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile Glu Gln Leu Lys
 485 490 495
 Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu Leu Gln Gly Asp
 500 505 510
 Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly Asn Ser Thr Arg
 515 520 525
 Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly Gln Val Gly Ala
 530 535 540
 Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu Asp Ala Gln Ile
 545 550 555 560
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 580 585 590

<210> 12
 <211> 1084
 <212> PRT
 <213> Homo sapiens

<400> 12
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 35 40 45
 Met Asp Leu Arg Leu Asp His Gln Phe Ser Leu Pro Val Ala Glu Pro
 50 55 60
 Ala Leu Arg Glu Gln Gln Leu Gln Gln Glu Leu Leu Ala Leu Lys Gln
 65 70 75 80
 Lys Gln Gln Ile Gln Arg Gln Ile Leu Ile Ala Glu Phe Gln Arg Gln
 85 90 95
 His Glu Gln Leu Ser Arg Gln His Glu Ala Gln Leu His Glu His Ile
 100 105 110
 Lys Gln Gln Gln Glu Met Leu Ala Met Lys His Gln Gln Glu Leu Leu

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610 615 620
 Arg Pro Leu Ser Arg Ala Gln Ser Ser Pro Ala Ser Ala Thr Phe Pro
 625 630 635 640
 Val Ser Val Gln Glu Pro Pro Thr Lys Pro Arg Phe Thr Thr Gly Leu
 645 650 655
 Val Tyr Asp Thr Leu Met Leu Lys His Gln Cys Thr Cys Gly Ser Ser
 660 665 670
 Ser Ser His Pro Glu His Ala Gly Arg Ile Gln Ser Ile Trp Ser Arg
 675 680 685
 Leu Gln Glu Thr Gly Leu Arg Gly Lys Cys Glu Cys Ile Arg Gly Arg
 690 695 700
 Lys Ala Thr Leu Glu Glu Leu Gln Thr Val His Ser Glu Ala His Thr
 705 710 715 720
 Leu Leu Tyr Gly Thr Asn Pro Leu Asn Arg Gln Lys Leu Asp Ser Lys
 725 730 735
 Lys Leu Leu Gly Ser Leu Ala Ser Val Phe Val Arg Leu Pro Cys Gly
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 755 760 765
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 785 790 795 800
 Gly His His Ala Glu Ser Thr Pro Met Gly Phe Cys Tyr Phe Asn
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 Ser Val Ala Val Ala Ala Lys Leu Leu Gln Gln Arg Leu Ser Val Ser
 820 825 830
 Lys Ile Leu Ile Val Asp Trp Asp Val His His Gly Asn Gly Thr Gln
 835 840 845
 Gln Ala Phe Tyr Ser Asp Pro Ser Val Leu Tyr Met Ser Leu His Arg
 850 855 860
 Tyr Asp Asp Gly Asn Phe Pro Gly Ser Gly Ala Pro Asp Glu Val
 865 870 875 880
 Gly Thr Gly Pro Gly Val Gly Phe Asn Val Asn Met Ala Phe Thr Gly
 885 890 895
 Gly Leu Asp Pro Pro Met Gly Asp Ala Glu Tyr Leu Ala Ala Phe Arg
 900 905 910
 Thr Val Val Met Pro Ile Ala Ser Glu Phe Ala Pro Asp Val Val Leu
 915 920 925
 Val Ser Ser Gly Phe Asp Ala Val Glu Gly His Pro Thr Pro Leu Gly
 930 935 940
 Gly Tyr Asn Leu Ser Ala Arg Cys Phe Gly Tyr Leu Thr Lys Gln Leu
 945 950 955 960
 Met Gly Leu Ala Gly Gly Arg Ile Val Leu Ala Leu Glu Gly Gly His
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 Asp Leu Thr Ala Ile Cys Asp Ala Ser Glu Ala Cys Val Ser Ala Leu
 980 985 990
 Leu Gly Asn Glu Leu Asp Pro Leu Pro Glu Lys Val Leu Gln Gln Arg
 995 1000 1005
 Pro Asn Ala Asn Ala Val Arg Ser Met Glu Lys Val Met Glu Ile His
 1010 1015 1020
 Ser Lys Tyr Trp Arg Cys Leu Gln Arg Thr Thr Ser Thr Ala Gly Arg
 1025 1030 1035 1040
 Ser Leu Ile Glu Ala Gln Thr Cys Glu Asn Glu Glu Ala Glu Thr Val
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19/25

<211> 3550

<212> DNA

<213> Homo sapiens

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gttctcttaa 3550

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23

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<400> 18

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23

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 645 650 655
 His Ala Gly Arg Ile Gln Ser Ile Trp Ser Arg Leu Gln Glu Thr Gly
 660 665 670
 Leu Leu Asn Lys Cys Glu Arg Ile Gln Gly Arg Lys Ala Ser Leu Glu
 675 680 685
 Glu Ile Gln Leu Val His Ser Glu His His Ser Leu Leu Tyr Gly Thr
 690 695 700
 Asn Pro Leu Asp Gly Gln Lys Leu Asp Pro Arg Ile Leu Leu Gly Asp
 705 710 715 720
 Asp Ser Gln Lys Phe Ser Ser Leu Pro Cys Gly Gly Leu Gly Val
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 Asp Ser Asp Thr Ile Trp Asn Glu Leu His Ser Ser Gly Ala Ala Arg
 740 745 750
 Met Ala Val Gly Cys Val Ile Glu Leu Ala Ser Lys Val Ala Ser Gly
 755 760 765
 Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro Gly His His Ala
 770 775 780
 Glu Glu Ser Thr Ala Met Gly Phe Cys Phe Phe Asn Ser Val Ala Ile
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 Thr Ala Lys Tyr Leu Arg Asp Gln Leu Asn Ile Ser Lys Ile Leu Ile
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 Val Asp Leu Asp Val His His Gly Asn Gly Thr Gln Gln Ala Phe Tyr
 820 825 830
 Ala Asp Pro Ser Ile Leu Tyr Ile Ser Leu His Arg Tyr Asp Glu Gly
 835 840 845
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<213> Homo sapiens

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<211> 967

<212> PRT

<213> Homo sapiens

<400> 6

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35     40     45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
50     55     60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
65     70     75     80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
85     90     95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
100    105    110
Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
115    120    125
Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
130    135    140
Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
145    150    155    160
Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
165    170    175
Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
180    185    190

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 Ser Ser Pro Gly Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly
 225 230 235 240
 Ser Val Thr Glu Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala
 245 250 255
 Glu Gln Met Val Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met
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 Asn Leu Leu Ser Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu
 275 280 285
 Gly Leu Pro Ala Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys
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 Glu Lys Gln Lys Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu
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 Pro Gly Gln Tyr Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His
 325 330 335
 Val Thr Leu Glu Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu
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 Ala Gly Gly Val Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu
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 Arg Ile Ser Pro Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg
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 Gln Leu Val Ile Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys
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 Gln Tyr Gln Gln Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile
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 Glu Gln Leu Lys Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu
 450 455 460
 Leu Gln Gly Asp Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly
 465 470 475 480
 Asn Ser Thr Arg Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly
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 Gln Val Gly Ala Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu
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 Asp Ala Gln Ile Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met
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 530 535 540
 Gln Ala Pro Leu Ala Ala Val Gly Met Asp Gly Leu Glu Lys His Arg
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 Tyr Asp Pro Leu Met Leu Lys His Gln Cys Val Cys Gly Asn Ser Thr
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 660 665 670
 Leu Leu Gly Asp Asp Ser Gln Lys Phe Phe Ser Ser Leu Pro Cys Gly
 675 680 685

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Gly Leu Gly Val Asp Ser Asp Thr Ile Trp Asn Glu Leu His Ser Ser
 690 695 700
 Gly Ala Ala Arg Met Ala Val Gly Cys Val Ile Glu Leu Ala Ser Lys
 705 710 715 720
 Val Ala Ser Gly Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro
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 Gly His His Ala Glu Glu Ser Thr Ala Met Gly Phe Cys Phe Phe Asn
 740 745 750
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 755 760 765
 Lys Ile Leu Ile Val Asp Leu Asp Val His His Gly Asn Gly Thr Gln
 770 775 780
 Gln Ala Phe Tyr Ala Asp Pro Ser Ile Leu Tyr Ile Ser Leu His Arg
 785 790 795 800
 Tyr Asp Glu Gly Asn Phe Phe Pro Gly Ser Gly Ala Pro Asn Glu Val
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 Gly Thr Gly Leu Gly Glu Gly Tyr Asn Ile Asn Ile Ala Trp Thr Gly
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 Gly Leu Asp Pro Pro Met Gly Asp Val Glu Tyr Leu Glu Ala Phe Arg
 835 840 845
 Thr Ile Val Lys Pro Val Ala Lys Glu Phe Asp Pro Asp Met Val Leu
 850 855 860
 Val Ser Ala Gly Phe Asp Ala Leu Glu Gly His Thr Pro Pro Leu Gly
 865 870 875 880
 Gly Tyr Lys Val Thr Ala Lys Cys Phe Gly His Leu Thr Lys Gln Leu
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 Met Thr Leu Ala Asp Gly Arg Val Val Leu Ala Leu Glu Gly Gly His
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 Asp Leu Thr Ala Ile Cys Asp Ala Ser Glu Ala Cys Val Asn Ala Leu
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<213> Homo sapiens

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35     40     45
Glu Leu Leu Leu Ile Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
50     55     60
Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
65     70     75     80
Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
85     90     95
Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
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Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
115    120    125

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Gly	Lys	Asp	Arg	Gly	Arg	Glu	Arg	Ala	Val	Ala	Ser	Thr	Glu	Val	Lys
130						135					140				
Gln	Lys	Leu	Gln	Glu	Phe	Leu	Leu	Ser	Lys	Ser	Ala	Thr	Lys	Asp	Thr
145					150					155					160
Pro	Thr	Asn	Gly	Lys	Asn	His	Ser	Val	Ser	Arg	His	Pro	Lys	Leu	Trp
			165						170					175	
Tyr	Thr	Ala	Ala	His	His	Thr	Ser	Leu	Asp	Gln	Ser	Ser	Pro	Pro	Leu
			180					185					190		
Ser	Gly	Thr	Ser	Pro	Ser	Tyr	Lys	Tyr	Thr	Leu	Pro	Gly	Ala	Gln	Asp
		195					200					205			
Ala	Lys	Asp	Asp	Phe	Pro	Leu	Arg	Lys	Thr	Glu	Ser	Ser	Val	Ser	Ser
		210				215					220				
Ser	Ser	Pro	Gly	Ser	Gly	Pro	Ser	Ser	Pro	Asn	Asn	Gly	Pro	Thr	Gly
225					230					235					240
Ser	Val	Thr	Glu	Asn	Glu	Thr	Ser	Val	Leu	Pro	Pro	Thr	Pro	His	Ala
				245					250					255	
Glu	Gln	Met	Val	Ser	Gln	Gln	Arg	Ile	Leu	Ile	His	Glu	Asp	Ser	Met
		260						265					270		
Asn	Leu	Leu	Ser	Leu	Tyr	Thr	Ser	Pro	Ser	Leu	Pro	Asn	Ile	Thr	Leu
		275					280					285			
Gly	Leu	Pro	Ala	Val	Pro	Ser	Gln	Leu	Asn	Ala	Ser	Asn	Ser	Leu	Lys
		290				295				300					
Glu	Lys	Gln	Lys	Cys	Glu	Thr	Gln	Thr	Leu	Arg	Gln	Gly	Val	Pro	Leu
305					310					315					320
Pro	Gly	Gln	Tyr	Gly	Gly	Ser	Ile	Pro	Ala	Ser	Ser	Ser	His	Pro	His
				325					330					335	
Val	Thr	Leu	Glu	Gly	Lys	Pro	Pro	Asn	Ser	Ser	His	Gln	Ala	Leu	Leu
			340					345					350		
Gln	His	Leu	Leu	Leu	Lys	Glu	Gln	Met	Arg	Gln	Gln	Lys	Leu	Leu	Val
		355				360						365			
Ala	Gly	Gly	Val	Pro	Leu	His	Pro	Gln	Ser	Pro	Leu	Ala	Thr	Lys	Glu
		370				375					380				
Arg	Ile	Ser	Pro	Gly	Ile	Arg	Gly	Thr	His	Lys	Leu	Pro	Arg	His	Arg
385					390					395					400
Pro	Leu	Asn	Arg	Thr	Gln	Ser	Ala	Pro	Leu	Pro	Gln	Ser	Thr	Leu	Ala
				405					410					415	
Gln	Leu	Val	Ile	Gln	Gln	Gln	His	Gln	Gln	Phe	Leu	Glu	Lys	Gln	Lys
			420					425					430		
Gln	Tyr	Gln	Gln	Gln	Ile	His	Met	Asn	Lys	Leu	Leu	Ser	Lys	Ser	Ile
		435					440					445			
Glu	Gln	Leu	Lys	Gln	Pro	Gly	Ser	His	Leu	Glu	Glu	Ala	Glu	Glu	Glu
		450				455					460				
Leu	Gln	Gly	Asp	Gln	Ala	Met	Gln	Glu	Asp	Arg	Ala	Pro	Ser	Ser	Gly
465					470					475					480
Asn	Ser	Thr	Arg	Ser	Asp	Ser	Ser	Ala	Cys	Val	Asp	Asp	Thr	Leu	Gly
				485					490					495	
Gln	Val	Gly	Ala	Val	Lys	Val	Lys	Glu	Glu	Pro	Val	Asp	Ser	Asp	Glu
			500					505					510		
Asp	Ala	Gln	Ile	Gln	Glu	Met	Glu	Ser	Gly	Glu	Gln	Ala	Ala	Phe	Met
		515					520					525			
Gln	Gln	Pro	Phe	Leu	Glu	Pro	Thr	His	Thr	Arg	Ala	Leu	Ser	Val	Arg
		530				535					540				
Gln	Ala	Pro	Leu	Ala	Ala	Val	Gly	Met	Asp	Gly	Leu	Glu	Lys	His	Arg
545					550					555					560
Leu	Val	Ser	Arg	Thr	His	Ser	Ser	Pro	Ala	Ala	Ser	Val	Leu	Pro	His
				565					570					575	
Pro	Ala	Met	Asp	Arg	Pro	Leu	Gln	Pro	Gly	Ser	Ala	Thr	Gly	Ile	Ala
				580				585					590		
Tyr	Asp	Pro	Leu	Met	Leu	Lys	His	Gln	Cys	Val	Cys	Gly	Asn	Ser	Thr
		595					600					605			
Thr	His	Pro	Glu	His	Ala	Gly	Arg	Ile	Gln	Ser	Ile	Trp	Ser	Arg	Leu
						615						620			

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Gln Glu Thr Gly Leu Leu Asn Lys Cys Glu Arg Ile Gln Gly Arg Lys
 625 630 635 640
 Ala Ser Leu Glu Glu Ile Gln Leu Val His Ser Glu His His Ser Leu
 645 650 655
 Leu Tyr Gly Thr Asn Pro Leu Asp Gly Gln Lys Leu Asp Pro Arg Ile
 660 665 670
 Leu Leu Gly Asp Asp Ser Gln Lys Phe Phe Ser Ser Leu Pro Cys Gly
 675 680 685
 Gly Leu Gly Val Asp Ser Asp Thr Ile Trp Asn Glu Leu His Ser Ser
 690 695 700
 Gly Ala Ala Arg Met Ala Val Gly Cys Val Ile Glu Leu Ala Ser Lys
 705 710 715 720
 Val Ala Ser Gly Glu Leu Lys Asn Gly Phe Ala Val Val Arg Pro Pro
 725 730 735
 Gly His His Ala Glu Glu Ser Thr Ala Met Gly Phe Cys Phe Phe Asn
 740 745 750
 Ser Val Ala Ile Thr Ala Lys Tyr Leu Arg Asp Gln Leu Asn Ile Ser
 755 760 765
 Lys Ile Leu Ile Val Asp Leu Asp Val His His Gly Asn Gly Thr Gln
 770 775 780
 Gln Ala Phe Tyr Ala Asp Pro Ser Ile Leu Tyr Ile Ser Leu His Arg
 785 790 795 800
 Tyr Asp Glu Gly Asn Phe Phe Pro Gly Ser Gly Ala Pro Asn Glu Val
 805 810 815
 Arg Phe Ile Ser Leu Glu Pro His Phe Tyr Leu Tyr Leu Ser Gly Asn
 820 825 830
 Cys Ile Ala
 835

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 <211> 1791
 <212> DNA
 <213> Homo sapiens

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 ggacgagagc agctcttggc tcagcaaaaga atgcacagta tgatcagctc agtggatgtg 180
 aagtcagaag ttccctgtggg cctggagccc atctcacctt tagacctaa gacagacctc 240
 aggatgatga tgcccgtggt ggacctgtt gtccgtgaga agcaattgca gcaggaatta 300
 cttcttatcc agcagcagca acaaatccag aagcagcttc tgatagcaga gtttcagaaa 360
 cagcatgaga acttgacacg gcagcaccag gctcagcttc aggagcatat caaggaactt 420
 ctagccataa aacagcaaca agaactccta gaaaaggagc agaaactgga gcagcagagg 480
 caagaacagg aagtagagag gcatcgagca gaacagcagc ttcctcctct cagaggcaaa 540
 gatagaggac gagaaagggc agtggcaagt acagaagtaa agcagaagct tcaagagttc 600
 ctactgagta aatcagcaac gaaagacact ccaactaatg gaaaaaatca ttccgtgagc 660
 cgccatccca agctctggta cacggctgcc caccacacat cattggatca aagctctcca 720
 ccccttagtg gaacatctcc atcctacaag tacacattac caggagcaca agatgcaaag 780
 gatgatttcc cccttcgaaa aactgaatcc tcagtcagta gcagttctcc aggctctggc 840
 cccagttcac caaacaatgg gccaactgga agtggtactg aaaatgagac ttcggttttg 900
 cccctacccc ctcatgccga gcaaatgggt tcacagcaac gcatttctaat tcatgaagat 960
 tccatgaacc tgctaagtct ttatacctct cttcttttgc ccaacattac cttggggctt 1020
 cccgcagtgc catccagct caatgcttcg aattcactca aagaaaagca gaagtgtgag 1080
 acgcagagcg ttaggcaagg tgttctctcg cctgggcagt atggaggcag catcccggca 1140
 tcttcagccc accctcatgt tacttttagag ggaaagccac ccaacagcag ccaccaggct 1200
 ctctgcagc atttattatt gaaagaacaa atgcgcagc aaaagcttct tgtagctggc 1260
 ggagttccct tacatcctca gtctcccttg gcaacaaaag agagaatttc acctggcatt 1320
 agaggtaccc acaaatggcc cgtcacaga cccctgaacc gaacccagtc tgcacctttg 1380
 cctcagagca cgttggctca gctggctcatt caacagcaac accagcaatt cttggagaag 1440
 cagaagcaat accagcagca gatccacatg aacaaactgc ttctgaaatc tattgaacaa 1500
 ctgaagcaac caggcagtca ccttgaggaa gcagaggaag agcttcaggg ggaccaggcg 1560

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atgcaggaag acagagcgcc ctctagtggc aacagcacta ggagcgacag cagtgccttgt 1620
 gtggatgaca cactgggaca agttggggct gtgaagggtca aggaggaacc agtggacagt 1680
 gatgaagatg ctcagatcca ggaaatggaa tctggggagc aggctgcttt tatgcaacag 1740
 gtaataggca aagatttagc tccaggattt gtaattaaag tcattatctg a 1791.

<210> 10

<211> 546

<212> PRT

<213> Homo sapiens

<400> 10

Met	His	Ser	Met	Ile	Ser	Ser	Val	Asp	Val	Lys	Ser	Glu	Val	Pro	Val
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Gly	Leu	Glu	Pro	Ile	Ser	Pro	Leu	Asp	Leu	Arg	Thr	Asp	Leu	Arg	Met
			20					25					30		
Met	Met	Pro	Val	Val	Asp	Pro	Val	Val	Arg	Glu	Lys	Gln	Leu	Gln	Gln
		35					40					45			
Glu	Leu	Leu	Leu	Ile	Gln	Gln	Gln	Gln	Ile	Gln	Lys	Gln	Leu	Leu	
	50					55				60					
Ile	Ala	Glu	Phe	Gln	Lys	Gln	His	Glu	Asn	Leu	Thr	Arg	Gln	His	Gln
65					70				75					80	
Ala	Gln	Leu	Gln	Glu	His	Ile	Lys	Glu	Leu	Leu	Ala	Ile	Lys	Gln	Gln
				85					90					95	
Gln	Glu	Leu	Leu	Glu	Lys	Glu	Gln	Lys	Leu	Glu	Gln	Gln	Arg	Gln	Glu
			100					105						110	
Gln	Glu	Val	Glu	Arg	His	Arg	Arg	Glu	Gln	Gln	Leu	Pro	Pro	Leu	Arg
		115					120					125			
Gly	Lys	Asp	Arg	Gly	Arg	Glu	Arg	Ala	Val	Ala	Ser	Thr	Glu	Val	Lys
	130					135						140			
Gln	Lys	Leu	Gln	Glu	Phe	Leu	Leu	Ser	Lys	Ser	Ala	Thr	Lys	Asp	Thr
145					150					155				160	
Pro	Thr	Asn	Gly	Lys	Asn	His	Ser	Val	Ser	Arg	His	Pro	Lys	Leu	Trp
			165						170					175	
Tyr	Thr	Ala	Ala	His	His	Thr	Ser	Leu	Asp	Gln	Ser	Ser	Pro	Pro	Leu
		180						185						190	
Ser	Gly	Thr	Ser	Pro	Ser	Tyr	Lys	Tyr	Thr	Leu	Pro	Gly	Ala	Gln	Asp
	195						200					205			
Ala	Lys	Asp	Asp	Phe	Pro	Leu	Arg	Lys	Thr	Glu	Ser	Ser	Val	Ser	Ser
	210					215					220				
Ser	Ser	Pro	Gly	Ser	Gly	Pro	Ser	Ser	Pro	Asn	Asn	Gly	Pro	Thr	Gly
225					230					235				240	
Ser	Val	Thr	Glu	Asn	Glu	Thr	Ser	Val	Leu	Pro	Pro	Thr	Pro	His	Ala
			245						250					255	
Glu	Gln	Met	Val	Ser	Gln	Gln	Arg	Ile	Leu	Ile	His	Glu	Asp	Ser	Met
		260						265					270		
Asn	Leu	Leu	Ser	Leu	Tyr	Thr	Ser	Pro	Ser	Leu	Pro	Asn	Ile	Thr	Leu
	275						280					285			
Gly	Leu	Pro	Ala	Val	Pro	Ser	Gln	Leu	Asn	Ala	Ser	Asn	Ser	Leu	Lys
	290					295					300				
Glu	Lys	Gln	Lys	Cys	Glu	Thr	Gln	Thr	Leu	Arg	Gln	Gly	Val	Pro	Leu
305					310					315				320	
Pro	Gly	Gln	Tyr	Gly	Gly	Ser	Ile	Pro	Ala	Ser	Ser	Ser	His	Pro	His
			325						330					335	
Val	Thr	Leu	Glu	Gly	Lys	Pro	Pro	Asn	Ser	Ser	His	Gln	Ala	Leu	Leu
		340						345					350		
Gln	His	Leu	Leu	Leu	Lys	Glu	Gln	Met	Arg	Gln	Gln	Lys	Leu	Leu	Val
	355					360						365			
Ala	Gly	Gly	Val	Pro	Leu	His	Pro	Gln	Ser	Pro	Leu	Ala	Thr	Lys	Glu
	370				375						380				
Arg	Ile	Ser	Pro	Gly	Ile	Arg	Gly	Thr	His	Lys	Leu	Pro	Arg	His	Arg
385					390					395				400	
Pro	Leu	Asn	Arg	Thr	Gln	Ser	Ala	Pro	Leu	Pro	Gln	Ser	Thr	Leu	Ala

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405 410 415
 Gln Leu Val Ile Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys
 420 425 430
 Gln Tyr Gln Gln Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile
 435 440 445
 Glu Gln Leu Lys Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu
 450 455 460
 Leu Gln Gly Asp Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly
 465 470 475 480
 Asn Ser Thr Arg Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly
 485 490 495
 Gln Val Gly Ala Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu
 500 505 510
 Asp Ala Gln Ile Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met
 515 520 525
 Gln Gln Val Ile Gly Lys Asp Leu Ala Pro Gly Phe Val Ile Lys Val
 530 535 540
 Ile Ile
 545

<210> 11
 <211> 590
 <212> PRT
 <213> Homo sapiens

<400> 11
 Met His Ser Met Ile Ser Ser Val Asp Val Lys Ser Glu Val Pro Val
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 Gly Leu Glu Pro Ile Ser Pro Leu Asp Leu Arg Thr Asp Leu Arg Met
 20 25 30
 Met Met Pro Val Val Asp Pro Val Val Arg Glu Lys Gln Leu Gln Gln
 35 40 45
 Glu Leu Leu Ile Gln Gln Gln Gln Ile Gln Lys Gln Leu Leu
 50 55 60
 Ile Ala Glu Phe Gln Lys Gln His Glu Asn Leu Thr Arg Gln His Gln
 65 70 75 80
 Ala Gln Leu Gln Glu His Ile Lys Glu Leu Leu Ala Ile Lys Gln Gln
 85 90 95
 Gln Glu Leu Leu Glu Lys Glu Gln Lys Leu Glu Gln Gln Arg Gln Glu
 100 105 110
 Gln Glu Val Glu Arg His Arg Arg Glu Gln Gln Leu Pro Pro Leu Arg
 115 120 125
 Gly Lys Asp Arg Gly Arg Glu Arg Ala Val Ala Ser Thr Glu Val Lys
 130 135 140
 Gln Lys Leu Gln Glu Phe Leu Leu Ser Lys Ser Ala Thr Lys Asp Thr
 145 150 155 160
 Pro Thr Asn Gly Lys Asn His Ser Val Ser Arg His Pro Lys Leu Trp
 165 170 175
 Tyr Thr Ala Ala His His Thr Ser Leu Asp Gln Ser Ser Pro Pro Leu
 180 185 190
 Ser Gly Thr Ser Pro Ser Tyr Lys Tyr Thr Leu Pro Gly Ala Gln Asp
 195 200 205
 Ala Lys Asp Asp Phe Pro Leu Arg Lys Thr Ala Ser Glu Pro Asn Leu
 210 215 220
 Lys Val Arg Ser Arg Leu Lys Gln Lys Val Ala Glu Arg Arg Ser Ser
 225 230 235 240
 Pro Leu Leu Arg Arg Lys Asp Gly Asn Val Val Thr Ser Phe Lys Lys
 245 250 255
 Arg Met Phe Glu Val Thr Glu Ser Ser Val Ser Ser Ser Ser Pro Gly
 260 265 270
 Ser Gly Pro Ser Ser Pro Asn Asn Gly Pro Thr Gly Ser Val Thr Glu

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275	280	285
Asn Glu Thr Ser Val Leu Pro Pro Thr Pro His Ala Glu Gln Met Val		
290	295	300
Ser Gln Gln Arg Ile Leu Ile His Glu Asp Ser Met Asn Leu Leu Ser		
305	310	315
Leu Tyr Thr Ser Pro Ser Leu Pro Asn Ile Thr Leu Gly Leu Pro Ala		
	325	330
		335
Val Pro Ser Gln Leu Asn Ala Ser Asn Ser Leu Lys Glu Lys Gln Lys		
	340	345
		350
Cys Glu Thr Gln Thr Leu Arg Gln Gly Val Pro Leu Pro Gly Gln Tyr		
	355	360
		365
Gly Gly Ser Ile Pro Ala Ser Ser Ser His Pro His Val Thr Leu Glu		
	370	375
		380
Gly Lys Pro Pro Asn Ser Ser His Gln Ala Leu Leu Gln His Leu Leu		
385	390	395
Leu Lys Glu Gln Met Arg Gln Gln Lys Leu Leu Val Ala Gly Gly Val		
	405	410
		415
Pro Leu His Pro Gln Ser Pro Leu Ala Thr Lys Glu Arg Ile Ser Pro		
	420	425
		430
Gly Ile Arg Gly Thr His Lys Leu Pro Arg His Arg Pro Leu Asn Arg		
	435	440
		445
Thr Gln Ser Ala Pro Leu Pro Gln Ser Thr Leu Ala Gln Leu Val Ile		
	450	455
		460
Gln Gln Gln His Gln Gln Phe Leu Glu Lys Gln Lys Gln Tyr Gln Gln		
465	470	475
Gln Ile His Met Asn Lys Leu Leu Ser Lys Ser Ile Glu Gln Leu Lys		
	485	490
		495
Gln Pro Gly Ser His Leu Glu Glu Ala Glu Glu Glu Leu Gln Gly Asp		
	500	505
		510
Gln Ala Met Gln Glu Asp Arg Ala Pro Ser Ser Gly Asn Ser Thr Arg		
	515	520
		525
Ser Asp Ser Ser Ala Cys Val Asp Asp Thr Leu Gly Gln Val Gly Ala		
	530	535
		540
Val Lys Val Lys Glu Glu Pro Val Asp Ser Asp Glu Asp Ala Gln Ile		
545	550	555
Gln Glu Met Glu Ser Gly Glu Gln Ala Ala Phe Met Gln Gln Val Ile		
	565	570
		575
Gly Lys Asp Leu Ala Pro Gly Phe Val Ile Lys Val Ile Ile		
	580	585
		590

<210> 12

<211> 1084

<212> PRT

<213> Homo sapiens

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	20
	25
Asp Val Ala Thr Ala Leu Pro Leu Gln Val Ala Pro Ser Ala Val Pro	
	35
	40
Met Asp Leu Arg Leu Asp His Gln Phe Ser Leu Pro Val Ala Glu Pro	
	50
	55
Ala Leu Arg Glu Gln Gln Leu Gln Gln Glu Leu Leu Ala Leu Lys Gln	
65	70
	75
Lys Gln Gln Ile Gln Arg Gln Ile Leu Ile Ala Glu Phe Gln Arg Gln	
	85
	90
His Glu Gln Leu Ser Arg Gln His Glu Ala Gln Leu His Glu His Ile	
	100
	105
Lys Gln Gln Gln Glu Met Leu Ala Met Lys His Gln Gln Glu Leu Leu	
	110

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115 120 125
 Glu His Gln Arg Lys Leu Glu Arg His Arg Gln Glu Gln Glu Leu Glu
 130 135 140
 Lys Gln His Arg Glu Gln Lys Leu Gln Gln Leu Lys Asn Lys Glu Lys
 145 150 155 160
 Gly Lys Glu Ser Ala Val Ala Ser Thr Glu Val Lys Met Lys Leu Gln
 165 170 175
 Glu Phe Val Leu Asn Lys Lys Lys Ala Leu Ala His Arg Asn Leu Asn
 180 185 190
 His Cys Ile Ser Ser Asp Pro Arg Tyr Trp Tyr Gly Lys Thr Gln His
 195 200 205
 Ser Ser Leu Asp Gln Ser Ser Pro Pro Gln Ser Gly Val Ser Thr Ser
 210 215 220
 Tyr Asn His Pro Val Leu Gly Met Tyr Asp Ala Lys Asp Asp Phe Pro
 225 230 235 240
 Leu Arg Lys Thr Ala Ser Glu Pro Asn Leu Lys Leu Arg Ser Arg Leu
 245 250 255
 Lys Gln Lys Val Ala Glu Arg Arg Ser Ser Pro Leu Leu Arg Arg Lys
 260 265 270
 Asp Gly Pro Val Val Thr Ala Leu Lys Lys Arg Pro Leu Asp Val Thr
 275 280 285
 Asp Ser Ala Cys Ser Ser Ala Pro Gly Ser Gly Pro Ser Ser Pro Asn
 290 295 300
 Asn Ser Ser Gly Ser Val Ser Ala Glu Asn Gly Ile Ala Pro Ala Val
 305 310 315 320
 Pro Ser Ile Pro Ala Glu Thr Ser Leu Ala His Arg Leu Val Ala Arg
 325 330 335
 Glu Gly Ser Ala Ala Pro Leu Pro Leu Tyr Thr Ser Pro Ser Leu Pro
 340 345 350
 Asn Ile Thr Leu Gly Leu Pro Ala Thr Gly Pro Ser Ala Gly Thr Ala
 355 360 365
 Gly Gln Gln Asp Thr Glu Arg Leu Thr Leu Pro Ala Leu Gln Gln Arg
 370 375 380
 Leu Ser Leu Phe Pro Gly Thr His Leu Thr Pro Tyr Leu Ser Thr Ser
 385 390 395 400
 Pro Leu Glu Arg Asp Gly Gly Ala Ala His Ser Pro Leu Leu Gln His
 405 410 415
 Met Val Leu Leu Glu Gln Pro Pro Ala Gln Ala Pro Leu Val Thr Gly
 420 425 430
 Leu Gly Ala Leu Pro Leu His Ala Gln Ser Leu Val Gly Ala Asp Arg
 435 440 445
 Val Ser Pro Ser Ile His Lys Leu Arg Gln His Arg Pro Leu Gly Arg
 450 455 460
 Thr Gln Ser Ala Pro Leu Pro Gln Asn Ala Gln Ala Leu Gln His Leu
 465 470 475 480
 Val Ile Gln Gln Gln His Gln Gln Phe Leu Glu Lys His Lys Gln Gln
 485 490 495
 Phe Gln Gln Gln Gln Leu Gln Met Asn Lys Ile Ile Pro Lys Pro Ser
 500 505 510
 Glu Pro Ala Arg Gln Pro Glu Ser His Pro Glu Glu Thr Glu Glu Glu
 515 520 525
 Leu Arg Glu His Gln Ala Leu Leu Asp Glu Pro Tyr Leu Asp Arg Leu
 530 535 540
 Pro Gly Gln Lys Glu Ala His Ala Gln Ala Gly Val Gln Val Lys Gln
 545 550 555 560
 Glu Pro Ile Glu Ser Asp Glu Glu Glu Ala Glu Pro Pro Arg Glu Val
 565 570 575
 Glu Pro Gly Gln Arg Gln Pro Ser Glu Gln Glu Leu Leu Phe Arg Gln
 580 585 590
 Gln Ala Leu Leu Leu Glu Gln Gln Arg Ile His Gln Leu Arg Asn Tyr
 595 600 605
 Gln Ala Ser Met Glu Ala Ala Gly Ile Pro Val Ser Phe Gly Gly His

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610	615	620
Arg Pro Leu Ser Arg	Ala Gln Ser Ser Pro	Ala Ser Ala Thr Phe Pro
625	630	635
Val Ser Val Gln Glu	Pro Pro Thr Lys Pro	Arg Phe Thr Thr Gly Leu
645	650	655
Val Tyr Asp Thr Leu	Met Leu Lys His Gln	Cys Thr Cys Gly Ser Ser
660	665	670
Ser Ser His Pro Glu	His Ala Gly Arg Ile	Gln Ser Ile Trp Ser Arg
675	680	685
Leu Gln Glu Thr Gly	Leu Arg Gly Lys Cys	Glu Cys Ile Arg Gly Arg
690	695	700
Lys Ala Thr Leu Glu	Glu Leu Gln Thr Val	His Ser Glu Ala His Thr
705	710	715
Leu Leu Tyr Gly Thr	Asn Pro Leu Asn Arg	Gln Lys Leu Asp Ser Lys
725	730	735
Lys Leu Leu Gly Ser	Leu Ala Ser Val Phe	Val Arg Leu Pro Cys Gly
740	745	750
Gly Val Gly Val Asp	Ser Asp Thr Ile Trp	Asn Glu Val His Ser Ala
755	760	765
Gly Ala Ala Arg Leu	Ala Val Gly Cys Val	Val Glu Leu Val Phe Lys
770	775	780
Val Ala Thr Gly Glu	Leu Lys Asn Gly Phe	Ala Val Val Arg Pro Pro
785	790	795
Gly His His Ala Glu	Glu Ser Thr Pro Met	Gly Phe Cys Tyr Phe Asn
805	810	815
Ser Val Ala Val Ala	Ala Lys Leu Leu Gln	Gln Arg Leu Ser Val Ser
820	825	830
Lys Ile Leu Ile Val	Asp Trp Asp Val His	His Gly Asn Gly Thr Gln
835	840	845
Gln Ala Phe Tyr Ser	Asp Pro Ser Val Leu	Tyr Met Ser Leu His Arg
850	855	860
Tyr Asp Asp Gly Asn	Phe Pro Gly Ser Gly	Ala Pro Asp Glu Val
865	870	875
Gly Thr Gly Pro Gly	Val Gly Phe Asn Val	Asn Met Ala Phe Thr Gly
885	890	895
Gly Leu Asp Pro Pro	Met Gly Asp Ala Glu	Tyr Leu Ala Ala Phe Arg
900	905	910
Thr Val Val Met Pro	Ile Ala Ser Glu Phe	Ala Pro Asp Val Val Leu
915	920	925
Val Ser Ser Gly Phe	Asp Ala Val Glu Gly	His Pro Thr Pro Leu Gly
930	935	940
Gly Tyr Asn Leu Ser	Ala Arg Cys Phe Gly	Tyr Leu Thr Lys Gln Leu
945	950	955
Met Gly Leu Ala Gly	Gly Arg Ile Val Leu	Ala Leu Glu Gly Gly His
965	970	975
Asp Leu Thr Ala Ile	Cys Asp Ala Ser Glu	Ala Cys Val Ser Ala Leu
980	985	990
Leu Gly Asn Glu Leu	Asp Pro Leu Pro Glu	Lys Val Leu Gln Gln Arg
995	1000	1005
Pro Asn Ala Asn Ala	Val Arg Ser Met Glu	Lys Val Met Glu Ile His
1010	1015	1020
Ser Lys Tyr Trp Arg	Cys Leu Gln Arg Thr	Thr Ser Thr Ala Gly Arg
1025	1030	1035
Ser Leu Ile Glu Ala	Gln Thr Cys Glu Asn	Glu Glu Ala Glu Thr Val
1045	1050	1055
Thr Ala Met Ala Ser	Leu Ser Val Gly Val	Lys Pro Ala Glu Lys Arg
1060	1065	1070
Pro Asp Glu Glu Pro	Met Glu Glu Pro Pro	Leu
1075	1080	

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<211> 3550

<212> DNA

<213> Homo sapiens

<400> 13

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- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (71) Applicant (*for all designated States except US*): SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH [US/US]; 1275 York Avenue, New York, NY 10021 (US).
- (72) Inventors; and
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- Published:
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WO 02/102984 A3

(54) Title: HDAC9 POLYPEPTIDES AND POLYNUCLEOTIDES AND USES THEREOF

(57) Abstract: The present invention features substantially pure HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), an HDRP(Δ NLS) polypeptides, and isolated nucleic acid molecules encoding those polypeptides. The present invention also features vectors containing HDAC9, HDAC9a, HDAC9(Δ NLS), HDAC9a(Δ NLS), and HDRP(Δ NLS) nucleic acid sequences, and cells containing those vectors.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/19054

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 9/78, 9/00, 9/14, 1/20, 15/00; C07H 21/04
US CL : 435/227, 183, 195, 252.3, 320.1; 536/23.2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/227, 183, 195, 252.3, 320.1; 536/23.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN AND WEST. Sequence search in Swissprot, EST, N-GeneSeq, PIR_71, SPTREMBL & issued US patents.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NAGASE et al. Prediction of Coding Sequences of Unidentified Human Genes. XI. The Complete Sequences of 100 New cDNA Clones from Brain Which Code for Large Proteins in Vitro. DNA Research November 1998, Vol 5, pages 277-286. See Table 1, Accession No. AB018287 is 58.8% similar to DNA sequence of SEQ ID NO : 1, claim 4 (g).	4
A, P	ZHOU et al. Cloning and Characterization of a histone deacetylase, HDAC9. PNAS, 11 September 2001, Vol. 98, No. 19, pages 10572-10577.	1-9, 29
A	WANG et al. HDAC4, a Human Histone Deacetylase Related to Yeast HDA1, Is a Transcriptional Corepressor. Molecular and Cellular Biology, November 1999, Vol. 19, No. 11, pages 7816-7827.	1-9, 29

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

Special categories of cited documents:	
* "A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"B" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"Z" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

30 October 2002 (30.10.2002)

Date of mailing of the international search report

13 MAR 2003

Name and mailing address of the ISA/US

Commissioner of Patents and Trademarks
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Washington, D.C. 20231

Facsimile No. (703)305-3230

Authorized officer

Tekchand Saidha

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/190 51

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-9 & 29 (SEQ ID NOS : 1 & 2)

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/19051

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-9, 29, drawn to isolated nucleic acid, the encoded protein and protein composition.

Group II, claim(s) 10, drawn to antibody.

Group III, claim(s) 11-13, drawn to a method of identifying a compound - modulate DNA expression.

Group IV, claim(s) 14-19, 33, drawn to a method of identifying a compound that modulate enzymatic activity.

Group V, claim(s) 20-25, 34, drawn to a method of identifying a compound that modulate transcriptional repression activity of the polypeptide.

Group VI, claim(s) 26-27, drawn to a method of identifying a compound that modulate expression of a nucleic acid molecule.

Group VII, claim(s) 28, drawn to a method of identifying a polypeptide that interacts with a polypeptide of claim 1 in a two-hybrid system.

Group VIII, claim(s) 30-32, drawn to a method of diagnosing a cell proliferation disease.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

1. SEQ ID NO : 1 and 2 [HDAC9].
2. SEQ ID NO : 3 and 4 [HDAC9a].
3. SEQ ID NO : 5 and 6 [HDAC9- Δ NLS].
4. SEQ ID NO : 7 and 8 [HDAC9a- Δ NLS].
5. SEQ ID NO : 9 and 10 [HDRP- Δ NLS].

The claims are deemed to correspond to the species listed above in the following manner:

Each of the claims listed in groups I-VIII correspond to each of the 5 species which are structurally distinct.

The following claim(s) are generic: 1-5.

The inventions listed as Groups I-VIII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I has a special technical feature of the nucleotide sequence encoding a specific histone deacetylase which Groups II-VIII do not share; Group II has a special technical feature of the antibody to a specific histone deacetylase which Groups I & III-VIII do not share; Groups III-VIII employ nucleic acid or polypeptide in various method of identifying compounds or polypeptides for distinct uses. Further, in view of 37 CFR 1.475 (b), when claims corresponding to different categories of inventions are present then only (3) applies and additional methods of use are deemed to lack unity.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The various species correspond to nucleic acid and polypeptide sequences which are structurally and in activity distinct from each other, therefore lack the same or corresponding special technical feature.